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"Development of a Computer Decision System for Women with BRCA1 or BRCA2 Mutations" is a project uses a decision support system to provide individualized information about the expected benefits of alternative cancer risk reduction strategies for women with either a BRCA1 or BRCA2 mutation. The educational booklet and decision support system that were previously developed, are presently being used in the randomized control trial (RCT). Currently, eligible women are being identified through out the Philadelphia and surround areas for enrollment in the RCT. This year we focused our attention on developing strategies to locate eligible women in order to increase enrollment in the RCT. Strategies include: contacting women who have been tested prior to the start of the RCT, placing advertisements in local newspapers to target high-risk women, and collaborating with various organizations. These strategies have resulted in a major increase in enrollment this year. Through these recruitment strategies, we are confident that we will reach our goal RCT enrollment by next year.

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Annual Progress Report 2002 **protocol#173600**

Development of A Decision Support System for Women with BRCA1 or BRCA2 Mutations

PI- Katrina Armstrong

Introduction

"Development of a Computer Decision Support System for Women with BRCA1 or BRCA2 Mutations" is a project that aims to develop a decision support system that provides individualized information about the expected benefits of alternative cancer risk reduction strategies for women with either a BRCA1 or BRCA2 mutation. For decision-making about cancer risk reduction by women with BRCA1 or BRCA2 mutations to be truly informed, decisions must be consistent with a woman's personal preferences and values. Such decisions ultimately can only be made by the woman involved - she is the only one able to adequately value the trade-offs among the benefits, risks, and costs of the alternative management strategies. The objective of this project is to develop and evaluate a Decision Support System (DSS) that will improve informed decision making by providing women with tailored, simplified information about the expected health outcomes of alternative decisions. Based on a Markov model, the DSS is easily updated with new epidemiological evidence to provide women with the most accurate and up-to-date information about their risk and expected outcomes. The individualized information generated by the Markov model simulations is printed out and sent home with the woman to review with family members and friends, if she wishes. We are currently accruing subjects to a randomized control trial to assess the outcomes of this DSS.

Body

Phase One: Development of Educational Booklet

Using the information gathered through several focus groups conducted from the fall of 1998 through the spring of 1999, the educational booklet was written and illustrated. Entitled "Health Care Options for Women at Risk for Breast and Ovarian Cancer," the booklet covers topics suggested by women who have either been counseled about being tested or have been tested for a BRCA1 or BRCA2 mutation. The illustrations completed by a medical illustrator at the University of Pennsylvania complement the text and aide in the understanding of the results of prophylactic surgeries. Drafts of the booklet were critically reviewed several times by an expert panel including Barbara Weber, MD, Andrea Eisen, MD, Jill Stopfer, MS and Kathleen Calzone, M.S.N. Importantly these reviews led to the addition of several sections including breast and ovarian cancer screening, hysterectomy, and implications for family members.

The book was then sent to 12 Cancer Risk Evaluation Program (CREP) patients to review for any content or organizational suggestions. Reaction from these women was overwhelmingly positive, and there were very few changes suggested. Minor grammatical and structural changes were made to clarify some content, but the booklet was otherwise unchanged. In August 2000, the text and illustrations were published in a spiral bound book and are currently being used as a part of the randomized control trial (RCT) that began in November 2000.

Since the publication of the booklet, we have added supplemental information, placed in the beginning of the booklet, which includes new information about BRCA1 and 2, and incorporates comments from women in the RCT. Since the booklet was originally created only for women who tested positive for the gene mutation, many of the comments came from positive women who have also been diagnosed with breast cancer. The supplement clarifies which information is specific to

BRCA positive women, and which information also relates to BRCA positive women with breast cancer (Appendix A) using recently published data in this field (1-5).

Phase Two: Development of the Decision Support System

Part A: Development of Decision Analytic Model

The decision analytic model has been completed. Important revisions included:

1. Because the majority of women who are found to carry a mutation in BRCA1 or BRCA2 have been previously diagnosed with breast cancer and these women still face many of the same decisions about cancer risk reduction as women without a cancer diagnosis (e.g. prophylactic surgery), the investigator team felt it was important to include women with a prior diagnosis of breast cancer in the trial. Thus, we substantially revised the model to allow tailoring to the presence or absence of a previous diagnosis of breast cancer. Because survival following a diagnosis of breast cancer depends upon the characteristics of the cancer (in particular, stage and node status), we developed individual survival functions for Stage 1 and Stage 2 node positive and node negative breast cancer, further tailoring the model simulations for women with a prior diagnosis to the characteristics of their individual tumors. Initial feedback from our expert panel suggested the survival curves for node positive women might create sufficient distress that would interfere with informed decision making. Thus, we have chosen to exclude node positive breast cancer patients from the trial.
2. To allow inclusion of women with a prior diagnosis of coronary heart disease and osteoporosis in the trial, we revised the model to allow simulations to be tailored to these prior diagnoses.
3. As a result of the focus groups of women from CREP, the investigator team and expert panel all felt that showing the effect of alternative management strategies on breast cancer incidence was necessary to help women make decisions about cancer risk reduction strategies. Thus,

we revised the model to allow accurate calculation of cumulative incidence curves for breast cancer among women without a prior diagnosis of breast cancer. To minimize information overload, we initially show women only the curves for overall mortality and breast cancer incidence, the ovarian cancer curves are shown if a woman has indicated interest.

4. We have validated the model by comparing the estimated life expectancy from the simulation model using population based incidence rates for breast and ovarian cancer with data from the National Center for Health Statistics. The life expectancy of a 50 year old woman at average cardiac risk who selects no therapy from the simulation is 31.68 years compared to 31.70 years estimated by the National Center for Health Statistics.

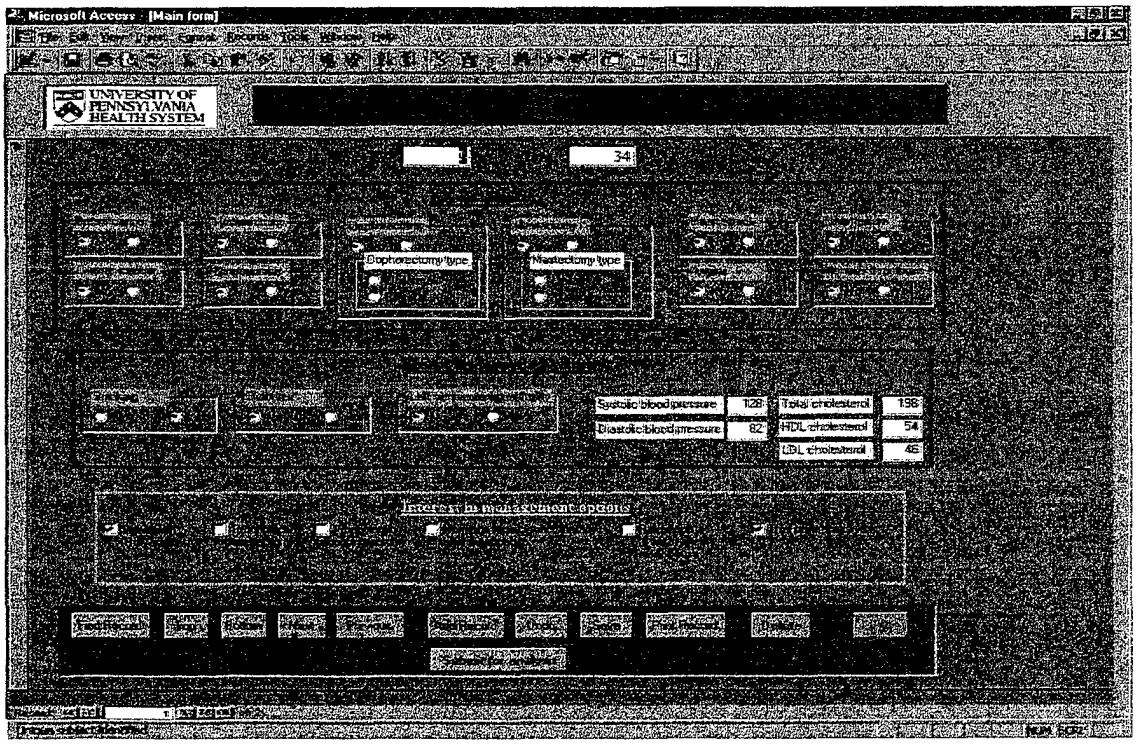
Part B: Format Effects

Using the data from the surveys conducted in past years, the survival curve materials have been adapted to the specific context relevant to women with BRCA mutations. This involved developing text that explains the concept of survival curves and how they should be interpreted. In order for the curves to be clear and organized, we developed a method of presenting the curves that allows each woman to see her options individually as well as together.

Each decision aid includes treatment option information as well as breast cancer incidence information. A baseline (no intervention) survival curve is fixed to a divider while the treatment options, each printed on transparencies, can be superimposed over the baseline curve. This layering effect allows the women to see the difference in survival between having no treatment (baseline) and the various treatment options, which can also be compared to each other. This method enables women to clearly distinguish which option gives her the best survival rate over time.

Part C: Continued Development of the Computer Interface

Between 1999 and 2000, the design and function of the computer interface for the decision support system was refined. This process required numerous meetings with project staff and with a focus group of nurses who have an interest in breast cancer research. After numerous iterations, a final design was implemented in Microsoft Access (shown below in the figure). The original platform (FoxPro) was abandoned, owing to difficulties with the transition to a client-server implementation that is expected in the future. The Access implementation will allow a seamless transition to a Web-based platform, although the focus now is on a single, standalone system. In addition, Access supports ActiveX objects through its extensive data model, and interfaces with the Data Interactive product from TreeAge Software. The interface for this system is shown below:



However, some difficulty in creating the interface between Data Interactive and the Access application has been encountered, forcing us to develop another system in parallel, so as not to delay the project. This second system provides an interface to the Markov model in DATA, using the interface builder in DATA software. While not ideal, in that it is not particularly attractive nor

does it support most of the usual Windows objects (such as buttons and panes), this second system will be used in place of the final software until the latter is fully implemented and debugged. The investigators are working with TreeAge to expedite the implementation of the Access-based system. Meanwhile, the second, simpler system has been tested and debugged, and has passed the scrutiny of the investigators and the focus group of nurses discussed above. Earlier this year (2002) there were some technical problems with the system, which resulted in a temporary halt in recruitment. But, fortunately these problems have been fixed, and the system is currently being used in the Randomized Control Trial.

Phase Three: Randomized Controlled Trial of Patient Decision Support System

The Randomized Control Trial (RCT) began with the enrollment of the first subject in November 2000. All questionnaires, booklet, decision aid, and model materials have been developed, produced, and implemented successfully in the RCT. All eligible subjects are contacted through CREP once their results are disclosed. The genetic counselors at CREP inform the patient about our study, giving them a letter introducing them to the project (Appendix B), and tell them that someone will be contacting them to see if they are interested in participating. Once informed that an eligible patient has been informed of her mutation, a staff member contacts her by phone to see if she would like to join the study. If the subject agrees, another staff member opens a randomization envelope to determine whether the subject will be in the control arm (booklet only) or the intervention arm (booklet and decision aid). The booklet is sent to all subjects along with the questionnaire "Assessment of Risk Factors & Interest in Risk Reduction Options"(Appendix C), which she is asked to complete and mail back. Upon receiving the completed questionnaire, a staff member will call the woman to schedule her visit.

When the subject comes in for her visit, at the beginning of the visit, she will complete the "Baseline Questionnaire" (Appendix D), which the staff member will take to record later. The visit

then begins with the staff member explaining that while this information is useful and represents a theoretical outcome of a woman like herself, it is not a certainty. The limitations of the staff member are also explained, noting that it is important that any specific questions about the subject's care be directed to her personal physicians. Once it is clear that the subject understands this, the staff member asks the subject if there are any questions about the content of the booklet, and whether she found it to be useful. Any comments are recorded at this time. If the subject has been randomized to the control arm, her visit is complete. She is advised that she will be called in a month to complete a follow up questionnaire (Appendix E) with another member of the staff.

If she is part of the intervention arm, the decision aid is reviewed next. To introduce the content of the decision aid, especially the survival and incidence curves, the woman is asked to complete a practice exercise to ensure that she understands the concept of survival curves. Once the subject is clear on what she is being shown, she is introduced to her survival and/or incidence curves. Beginning with the baseline survival curve, the staff member shows the subject her baseline curve, representing her outcome if she takes no action to change her risk. Then she is shown the curves that are both interesting to her as well as options for her. When she has seen the single options, she is shown curves representing her management options in combination. If the woman does not currently have breast cancer, she is next shown incidence curves in the same manner that she viewed the survival curves. Throughout the review process, she is asked questions to make sure that she understands what she is seeing as well as having her own questions answered to the best of the staff member's knowledge. When the decision aid has been reviewed and all questions answered, the subject is told that a staff member will be calling her in a month to complete a follow up survey.

To date, there have been twenty-one subjects enrolled in the study, twenty have sent back the "Assessment of Risk Factors & Interest in Risk Reduction Options" questionnaire, seventeen

have completed the interview session, and thirteen have completed the follow-up telephone questionnaire. Although the recruitment rate is lower than we had envisioned, we have seen a major increase in subjects enrolled. As of January 2002 there were still only two completed interviews. This low recruitment rate is due to several factors. Low numbers include a slower than anticipated uptake of testing for the BRCA1 and BRCA2 mutations in general, and specifically among cancer free men and women. The majority of women who are testing positive for the presence of a BRCA1 or BRCA2 mutation have already been diagnosed with breast or ovarian cancer, and are undergoing treatment. Thus the number of healthy women who are being tested in order to understand their personal and familial risks is limited to a small minority. Furthermore, the rate of women testing positive is much lower than expected.

We have explored many possibilities for increasing enrollment, and we are currently acting on several options. Patients who tested positive for a mutation through CREP before this study began were contacted to see if they were interested in participating. However, many had taken some action to manage their risk since being tested, deeming them not eligible for the study. Currently, CREP is offering a free test to men and women in families where a mutation is known to be present, which will provide us with a new group of healthy women who are likely to be BRCA1 or BRCA2 mutation carriers. Another option involves expanding to other hospitals within the Philadelphia area that have a genetic testing program. This has already begun at the University of Pennsylvania-owned Pennsylvania Hospital, and we have been successful enrolling subjects from this genetic testing program. Eventually, if it is deemed necessary, we will investigate recruiting women from other University of Pennsylvania-owned sites. Recently we met with Administrative Director, Jeanne Rogers, R.N., M.Ed. and coordinator Mary Sharon Rumsey, R.N., M.SN. of the Cancer Network. Collaborating with the Cancer Network, which is part of the University of Pennsylvania Cancer, is the first step to recruit women from other University of Pennsylvania-

owned sites. Finally, if needed, we will expand to sites outside of Philadelphia where there is already a collaborative relationship in place.

We have also investigated ways to recruit women from high-risk populations. We focused on Ashkenazi Jewish communities, since characteristic BRCA1 and BRCA2 mutations are more frequent in this population. Recently we placed an advertisement (Appendix F) in four local Jewish newspapers: Jewish Exponent, Main Line Times, Jewish Community Voice, and Jewish Voice. We also placed the ad in 15 local Jewish temple and synagogue newsletters. The advertisements ran for 1-2 months depending on newspaper prices. The majority of temples and synagogues allowed us to run our ad for free.

We have also collaborated with various organizations to recruit eligible women. In April of 2002 we posted an announcement about the study on Facing Our Risk of Cancer Empowered website's message board (www.facingourrisk.org). This site provides information and support for women who have or are at high-risk for the BRCA 1 or 2 mutations.

At a recent conference for young breast cancer survivors, sponsored by the organization Living Beyond Breast Cancer, we distributed flyers to members. Through these recruiting techniques we have received a number of calls from women interested and willing to participate in the study.

In summary, the past year we dedicated a great deal of time to improving recruitment rates. As a result there has been an increased enrollment of women in the RCT compared to past years. This enrollment increase can be attributed to the multiply strategies, collaborating with other sites and organizations, placing advertisements in local papers, and targeting high-risk groups. The technical problems with the DSS at the beginning of 2002 resulted in a temporary halt in recruitment, but once the problem was fixed we were able to continue our focus on increasing

enrollment. Currently we continue to actively recruit and enroll eligible women in the RCT, with expectations to reach our enrollment goal by early next spring.

Key Research Accomplishments

Computerized Decision Support System (CDSS) Development

- Linking of the model to the interface was completed in October 2000.
- The CDSS has been implemented successfully for use in the Randomized Control Trial.

Booklet Development

- Booklet completed and published August 2000.

Randomized Control Trial

- Decision Aid developed and published.
- RCT underway with patients currently being enrolled.
    - 21 women enrolled in the study.
    - 20 women returned and completed assessment of risk questionnaires.
    - 17 women completed visits and baseline questionnaires.
    - 13 women completed follow-up telephone questionnaire.
    - 2 women currently scheduled for visits this summer.
- Advertising to high-risk groups as a way to increase enrollment.
- Possibility of expanding to other testing sites within the Philadelphia area and further, as needed.

Reportable Outcomes

Published Manuscripts (Appendix G)

- Armstrong K, Schwartz JS, FitzGerald G, Ubel P. Effect of Framing as Gain vs. Loss on Hypothetical Treatment Choices: Survival and Mortality Curves. Medical Decision Making, Jan-Feb 2002: 76-83.

- Armstrong K, FitzGerald G, Schwartz SJ, Ubel PA. Using survival curve comparisons to inform patient decision making: Can a practice exercise improve understanding? J Gen Intern Med. 2001;16:482-485.

- Armstrong K, Chen T, Albert D, Schwartz SJ. Cost-Effectiveness Analysis of Raloxifene and Hormone Replacement Therapy in Postmenopausal Women. Obstetrics and Gynecology. 2001;98(6): 996-1003.

- Armstrong K, Calzone K, Stopfer J, FitzGerald G, Coyne J, Weber B. Factors associated with decisions about clinical BRCA1/2 testing. Cancer Epidemiol Biomarkers Prev. 2000;9:1251-1254.

Conclusions

This year we have seen a major increase in the enrollment of subjects in the randomized control trial (RCT). Our efforts to increase enrollment have been positive, and we will continue to explore more options to keep moving in this direction for the following year. Most recently we have recruited eligible women at a rate of 4 subjects per month. At this rate we are confident that we will reach our enrollment goal by spring 2003. Over the past year we have received feedback, including content clarity and need for up-to-date information, from subjects in the RCT. This feedback has been used to update the booklet and decision aid. Both booklet and decision aid continue to be used successfully with subjects enrolled in the RCT. Our goal for the next year is to complete recruitment for the RCT and begin data analysis.

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(1) Marchbanks PA, McDonald JA, Wilson, HG, et al. Oral contraceptives and the risk of breast cancer. N Engl J Med 2002;346:2025-32.

(2) Women's Health Initiative. Risks and benefits of estrogen plus progestin in healthy postmenopausal women. JAMA 2002;288:321-333.

(3) Kinsinger LS, Harris R, Woolf SH, et al. Chemoprevention of breast cancer: a summary of the evidence for the U.S. Preventive Services Task Force. Ann Intern Med 2002;137:59-67.

(4) Kauff ND, Satagopan JM, Robson ME, et al. Risk-reducing salpingo-oophorectomy in women with a BRCA1 or BRCA2 mutation. N Engl J Med 2002;346:1609-15.

(5) Rebbeck TR, Lynch HT, Neuhausen SL, et al. Prophylactic oophorectomy in carriers of BRCA1 or BRCA2 mutations. N Engl J Med 2002;346:1616-22.

Appendix A
Booklet Supplement

Booklet Update

Since the publication of Health Care Options for Women at Risk for Breast and Ovarian Cancer in 2000, scientist continue to learn more about BRCA1 and BRCA2 mutations. In order to provide you with the most recent information we have added this supplement to the booklet.

The information in this booklet was designed to help women with a BRCA 1 or 2 mutation make decisions about managing future cancer risk. For women with a current diagnosis of breast cancer, this information may not be directly relevant to their decisions about current cancer treatment. For example the role of tamoxifen for breast cancer prevention is different from the role of tamoxifen for breast cancer treatment, and these differences should be discussed with your doctor.

Recent data from a randomized control trial among healthy, postmenopausal women with a uterus showed that hormone replacement, with estrogen and progestin, slightly increases the risk of coronary disease and breast cancer, and decreases the risk of bone fractures. The use of hormone replacement therapy (HRT) in women with a uterus is no longer thought to increase overall life expectancy.

Recent findings from a study about oral contraceptives and breast cancer risk has shown that current and former oral-contraceptive use among women 35-64 years of age does not increase the risk of breast cancer.

Even at the time of this update, the medical community continues to learn more about BRCA1 and BRCA2 mutations, and new options for managing cancer risk may become available at anytime. Regular contact with health care providers can keep women with BRCA 1 or BRCA2 mutation up to date of new information.

Appendix B
Study Letter

UNIVERSITY OF
PENNSYLVANIA
HEALTH SYSTEM

Department of Medicine
Division of General Internal Medicine

Project: DAWN

July 30, 2002

Dear XX,

We have begun a new study at the Cancer Risk Evaluation Program that we believe you may be interested in participating. This study, "Decision Aid for Women Navigating Cancer Risk," aims to improve the information that women with either a BRCA1 or BRCA2 mutation receive about their risk management options. Because managing your risk is a complex decision, involving complicated information, we are constantly searching for new and better ways to help women with a BRCA mutation understand their options for cancer risk management. By participating in this study, you will receive extra information to help you manage your risk of developing breast or ovarian cancer. Participating in this study will not affect your eligibility for studies involving new cancer risk management options.

We will contact you within the next two weeks to answer any questions you may have about this study and to see if you are interested in participating. Please feel free to contact the research coordinator, Nikki, at 215-573-7907 if you would like to learn more about the study sooner. If you agree to participate we will send you additional material for review covering the many options available to women of your status. If you choose not to participate, your health care will in no way be compromised, as this is a voluntary study. We look forward to speaking with you in the near future.

Sincerely,

Katrina Armstrong

Barbara L. Weber

Katrina Armstrong, MD

Barbara Weber, MD

Nikki Peters

Nikki Peters

Appendix C
Assessment of Risk Questionnaire

Decision Aid for Women Navigating Cancer Study (DAWN)

Assessment of Risk Factors & Interest in Risk Reduction Options

Please answer the following questions about your personal medical history as well as your interest in risk reduction options. Thank you.

1. Name_____

   Daytime Phone Number _____

   Age_____

2. Do you have high blood pressure? ☐ Yes ☐ No ☐ Not sure

   What was your most recent blood pressure reading (if known)? _____

   Do you take medication for high blood pressure? ☐ Yes ☐ No ☐ Not sure

3. Do you have diabetes? ☐ Yes ☐ No ☐ Not sure

4. Do you have high cholesterol? ☐ Yes ☐ No ☐ Not sure

   What was your most recent cholesterol reading (if known)? Total: _____

   LDL ("bad cholesterol"): _____

   HDL ("good cholesterol"):_____

   Do you take medication for high cholesterol? ☐ Yes ☐ No ☐ Not sure

5. Do you smoke cigarettes? ☐ Yes ☐ No ☐ Not sure

   If yes: How many cigarettes do you smoke a day? _____

6. Have you ever had a heart attack? ☐ Yes ☐ No ☐ Not sure

   Have you ever had angina? ☐ Yes ☐ No ☐ Not sure

   Do you take medication for heart disease? ☐ Yes ☐ No ☐ Not sure

7. Have you ever had breast cancer? ☐ Yes ☐ No ☐ Not sure

   If yes, was it node positive or node negative?

   ☐ Node positive ☐ Node negative ☐ Not sure

8. Have you ever had ovarian cancer? ☐ Yes ☐ No ☐ Not sure

9. Do you have osteoporosis? ☐ Yes ☐ No ☐ Not sure

Please answer the following questions about your interest in some options for managing your health by circling one number for each question below.

1. Are you interested in participating in clinical trials (research studies) of investigational cancer risk reducing treatments?

1	2	3	4	5
Not at all interested				Extremely interested

2. Are you interested in having a prophylactic mastectomy?

1	2	3	4	5
Not at all interested				Extremely interested

3. Are you interested in having a prophylactic oophorectomy?

1	2	3	4	5
Not at all interested				Extremely interested

4. Are you interested in taking tamoxifen (Nolvadex™) for cancer risk reduction?

1	2	3	4	5
Not at all interested				Extremely interested

5. Are you interested in taking hormone replacement therapy after menopause?

1	2	3	4	5
Not at all interested				Extremely interested

6. Are you interested in taking raloxifene (Evista™) after menopause?

1	2	3	4	5
Not at all interested				Extremely interested

Appendix D
Baseline Questionnaire

Decision Aid for Women Navigating Cancer Study (DAWN)

Women found to have a BRCA1 or BRCA2 mutation are faced with many options for managing their risk of developing breast and/or ovarian cancer. These management options range from taking tamoxifen (Nolvadex™) to having a prophylactic mastectomy. In addition, women entering menopause may be faced with decisions about therapies such as hormone replacement therapy (HRT) or raloxifene (Evista™) that may also affect their risk of osteoporosis and heart disease.

Now, thinking about the choices that you may be facing, please look at the following comments other people have made. Please circle the number from 1 (strongly agree) to 5 (strongly disagree) that best shows how you feel about the decisions you are facing.

	Strongly agree	Agree	Neither agree nor disagree	Disagree	Strongly disagree
These decisions are hard for me to make.	1	2	3	4	5
I'm unsure what to do in this situation.	1	2	3	4	5
It's clear which choices are best for me.	1	2	3	4	5
I'm aware of the management options I have to modify my risk.	1	2	3	4	5
I feel I know the benefits of the management options for my risk.	1	2	3	4	5
I am satisfied that I am adequately informed about the issues important to my decision.	1	2	3	4	5
I feel I know the risks and side effects of the management options for my risk.	1	2	3	4	5
I have the right amount of support from others in my decision making process.	1	2	3	4	5
I feel I am making an informed choice.	1	2	3	4	5
My decision shows what is most important for me.	1	2	3	4	5
I expect to stick with my decision.	1	2	3	4	5
I am satisfied that these are my decisions to make.	1	2	3	4	5
I expect to successfully carry out the decisions that I am making.	1	2	3	4	5
I am satisfied that my decisions are consistent with my personal values.	1	2	3	4	5
The decisions that I am making are the best possible for me personally.	1	2	3	4	5

For the next set of items, please tell us whether you strongly disagree, somewhat disagree, neither agree nor disagree, somewhat agree, or strongly agree.

	Strongly disagree	Somewhat disagree	Neither agree nor disagree	Somewhat agree	Strongly agree
The important medical decisions should be made by your doctor, not by you.					
You should go along with your doctor's advice even if you disagree with it.					
When hospitalized, you should not be making decisions about your own care.					
You should feel free to make decisions about everyday medical problems.					
If you were sick, as your illness became worse, you would want your doctor to take greater control.					
You should decide how frequently you need a check up.					

Now suppose you developed a sore throat, stuffy nose, and cough that lasted for three days. You are about to call your doctor on the telephone. Who should make the following decisions? Should it be you alone, mostly you, the doctor and you equally, mostly the doctor, or the doctor alone?

	You alone	Mostly you	Doctor & you equally	Mostly doctor	Doctor alone
Whether you should be seen by a doctor.					
Whether a chest x-ray should be taken.					
Whether you should try taking cough syrup.					

Suppose you went to your doctor for a routine physical examination and he or she found that everything was all right except that your blood pressure was high (170/100). Who should make the following decisions? Should it be you alone, mostly you, the doctor and you equally, mostly the doctor, or the doctor alone?

	You alone	Mostly you	Doctor & you equally	Mostly doctor	Doctor alone
When the next visit to check your blood pressure should be.					
Whether you should take time off from work to relax.					
Whether you should be treated with medication or diet.					

Suppose you had an attack of severe chest pain that lasted for almost an hour, frightening you enough so that you went to the emergency room. In the emergency room the doctors discovered that you are having a heart attack. Your own doctor is called and you are taken up to the intensive care unit. Who should make the following decisions? Should it be you alone, mostly you, the doctor and you equally, mostly the doctor or the doctor alone?

	You alone	Mostly you	Doctor & you equally	Mostly doctor	Doctor alone
How often the nurses should wake you up to check your temperature and blood pressure.					
Whether you may have visitors aside from your immediate family.					
Whether a cardiologist should be consulted.					

For the next set of items, please tell us whether you strongly disagree, somewhat disagree, neither agree nor disagree, somewhat agree, or strongly agree.

	Strongly disagree	Somewhat disagree	Neither agree nor disagree	Somewhat agree	Strongly agree
As you become sicker you should be told everything about your illness.					
You should understand completely what is happening inside your body as a result of your illness.					
Even when news is bad, you should be well informed.					
Your doctor should explain the purpose of your laboratory tests.					
You should be given information only when you ask for it.					
It is important for you to know all the side effects of your medication.					
Information about your illness is as important as your treatment.					
When there is more than one method to treat a problem, you should be told about each one.					

Please check the appropriate box next to the statement about you during the past week:

	Rarely/none of the time (<1/ day)	Occasionally/ little of the time (1-2 days)	Some/ moderate amount of time (3-4 days)	Most/ all of the time (5-7 days)
I was bothered by things that don't usually bother me.				
I did not feel like eating; my appetite was poor.				
I felt that I could not shake the blues even with help from my family and friends.				
I felt that I was just as good as other people.				
I had trouble keeping my mind on what I was doing.				
I felt depressed.				
I felt that everything that I did was an effort.				
I felt hopeful about the future.				
I thought that my life had been a failure.				
I felt fearful.				
My sleep was restless				
I was happy.				
I talked less than usual.				
I felt lonely.				
People were unfriendly.				
I enjoyed life.				
I had crying spells.				
I felt sad.				
I felt that people dislike me.				
I could not get "going."				

The next questions ask about what you think about your risk of developing cancer or heart disease.

What do you believe is your chance of developing breast cancer by age 70 if you have yearly mammograms, but choose not to have prophylactic surgery, take tamoxifen, or take HRT (Hormone Replacement Therapy) or raloxifene after menopause?_____%

...How about if you do have a prophylactic mastectomy? _____%

...How about if you do have a prophylactic oophorectomy? _____%

...How about if you do take tamoxifen? _____%

...How about if you do take HRT after menopause? _____%

...How about if you do raloxifene after menopause? _____%

What do you believe your chance of developing ovarian cancer is by age 70 if you choose not to have a prophylactic oophorectomy? _____%

...How about if you do have a prophylactic oophorectomy? _____%

What do you believe your chance of developing heart disease by age 70 is if you choose not to take HRT or raloxifene at the onset of menopause? _____%

...How about if you do take HRT at the onset of menopause? _____%

...How about if you do take raloxifene at the onset of menopause? _____%

The next questions are about comments made by people concerned about breast cancer (BC), and/or ovarian cancer (OC). Please tell us how frequently these comments were true for you during the past week.

During the past week:	Not at all	Rarely	Sometimes	Often
You thought about BC and/or OC when you didn't mean to.				
You had trouble falling asleep or staying asleep because of pictures or thoughts about BC and/or OC that came into your mind.				
You had waves of strong feelings about BC and/or OC.				
You had dreams about BC and/or OC.				
Pictures about BC and/or OC popped into your mind.				
Any reminder brought back feelings about BC and/or OC.				

Please answer the following questions about some management options that you may have heard of.

Prophylactic Mastectomy (preventative removal of the breasts)

Have you had a prophylactic mastectomy? ☐ Yes ☐ No ☐ Not sure

If not, are you thinking about having a prophylactic mastectomy:

In the next month? ☐ Yes ☐ No ☐ Not sure

In the next 6 months? ☐ Yes ☐ No ☐ Not sure

In the future? ☐ Yes ☐ No ☐ Not sure

Prophylactic Oophorectomy (preventative removal of the ovaries)

Have you had a prophylactic oophorectomy? ☐ Yes ☐ No ☐ Not sure

If not, are you thinking about having a prophylactic oophorectomy:

In the next month? ☐ Yes ☐ No ☐ Not sure

In the next 6 months? ☐ Yes ☐ No ☐ Not sure

In the future? ☐ Yes ☐ No ☐ Not sure

Tamoxifen (Nolvadex™) for breast cancer prevention

Are you taking tamoxifen? ☐ Yes ☐ No ☐ Not sure

If not, are you thinking about taking tamoxifen:

In the next month ☐ Yes ☐ No ☐ Not sure

In the next 6 months? ☐ Yes ☐ No ☐ Not sure

In the future? ☐ Yes ☐ No ☐ Not sure

Hormone Replacement Therapy (HRT) after menopause

Are you taking HRT? ☐ Yes ☐ No ☐ Not sure

If not, are you thinking about taking HRT:

In the next month? ☐ Yes ☐ No ☐ Not sure

In the next 6 months? ☐ Yes ☐ No ☐ Not sure

At the time of menopause? ☐ Yes ☐ No ☐ Not sure

Raloxifene (Evista™) after menopause

Are you taking raloxifene? ☐ Yes ☐ No ☐ Not sure

If not, are you thinking about taking raloxifene:

In the next month?	☐ Yes	☐ No	☐ Not sure
In the next 6 months?	☐ Yes	☐ No	☐ Not sure
At the time of menopause?	☐ Yes	☐ No	☐ Not sure

Appendix E
Follow-up Questionnaire

Outcomes of Decision Aid for Women Navigating Cancer Study (DAWN)

As you know, women found to have a BRCA1 or BRCA2 mutation are faced with many options for managing their risk of developing breast and/or ovarian cancer. You have read and heard about many of your management options, now, thinking about the choices that you are making, please answer the following questions about some management options that are available to you.

Participating in Clinical Trials of Investigational Options for Managing Cancer Risk

1. Have you joined a research study of investigational treatments for reducing cancer risk (such as the STAR trial)? ☐ Yes ☐ No ☐ Not sure

If not, are you thinking about participating in a research study of new treatments:

☐ Yes ☐ No ☐ Not sure

Prophylactic Mastectomy (preventative removal of the breasts)

2a. Which of the following best describes your decision about prophylactic mastectomy:

☐ I never considered having a prophylactic mastectomy.

☐ I have decided against having a prophylactic mastectomy.

☐ I am considering having a prophylactic mastectomy.

☐ I am planning on having a prophylactic mastectomy at a later date.

☐ I have had or am scheduled to have a prophylactic mastectomy.

☐ Other: _____

2b. Which best describes your physician's recommendation for this option:

☐ Strongly in favor for a prophylactic mastectomy.

☐ Slightly in favor for a prophylactic mastectomy.

☐ Neither in favor for or against a prophylactic mastectomy.

☐ Slightly against a prophylactic mastectomy.

☐ Strongly against a prophylactic mastectomy.

Prophylactic Oophorectomy (preventative removal of ovaries)

3a. Which of the following best describes your decision about prophylactic oophorectomy:

☐ I never considered having a prophylactic oophorectomy.

☐ I have decided against having a prophylactic oophorectomy.

☐ I am considering having a prophylactic oophorectomy.

☐ I am planning on having a prophylactic oophorectomy at a later date.

☐ I have had or am scheduled to have a prophylactic oophorectomy.

☐ Other: _____

3b. Which best describes your physician's recommendation for this option:

☐ Strongly in favor for a prophylactic oophorectomy.

☐ Slightly in favor for a prophylactic oophorectomy.

☐ Neither in favor for or against a prophylactic oophorectomy.

☐ Slightly against a prophylactic oophorectomy.

☐ Strongly against a prophylactic oophorectomy.

Tamoxifen (Nolvadex™) for breast cancer prevention

4a. Which of the following best describes your decision about Tamoxifen:

☐ I never considered taking Tamoxifen.

☐ I have decided against taking Tamoxifen.

☐ I am currently considering taking Tamoxifen.

☐ I am planning on taking Tamoxifen at a later date.

☐ I am taking Tamoxifen.

☐ Other: _____

4b. Which best describes your physician's recommendation for this option:

☐ Strongly in favor for Tamoxifen.

☐ Slightly in favor for Tamoxifen.

☐ Neither in favor for or against Tamoxifen.

☐ Slightly against Tamoxifen.

☐ Strongly against Tamoxifen.

Hormone Replacement Therapy (HRT) after menopause

5a. Which of the following best describes your decision about Hormone Replacement Therapy (HRT):

☐ I never considered taking HRT.

☐ I have decided against taking HRT.

☐ I am currently considering taking HRT.

☐ I am planning on taking HRT at a later date.

☐ I am taking HRT.

☐ Other: _____

5b. Which best describes your physician's recommendation for this option:

☐ Strongly in favor for HRT.

☐ Slightly in favor for HRT.

☐ Neither in favor for or against HRT .

☐ Slightly against HRT.

☐ Strongly against HRT.

Raloxifene (Evista™) after menopause

6a. Which of the following best describes your decision about Raloxifene:

☐ I never considered taking Raloxifene.

☐ I have decided against taking Raloxifene.

☐ I am currently considering taking Raloxifene.

☐ I am planning on taking Raloxifene at a later date.

☐ I am taking Raloxifene.

☐ Other: _____

6b. Which best describes your physician's recommendation for this option:

☐ Strongly in favor for Raloxifene.

☐ Slightly in favor for Raloxifene.

☐ Neither in favor for or against Raloxifene.

☐ Slightly against Raloxifene.

☐ Strongly against Raloxifene.

7. Overall where do you feel you are in your decision making process?

☐ I have not thought about my options for managing my breast cancer risk.

☐ I have just begun to think about my options for managing my breast cancer risk.

☐ I am deciding on how to manage my breast cancer risk.

☐ I have decided how to manage my breast cancer risk.

8. Please tell me how many times you have thought about each statement during the past week:

Was it Rarely/None of the time, Occasionally, Somewhat, or most of the time?

	Rarely/none of the time (<1/ day)	Occasionally/ little of the time (1-2 days)	Some/ moderate amount of time (3-4 days)	Most/ all of the time (5-7 days)
a. I was bothered by things that don't usually bother me.				
b. I did not feel like eating; my appetite was poor.				
c. I felt that I could not shake the blues even with help from my family and friends.				
d. I felt that I was just as good as other people.				
e. I had trouble keeping my mind on what I was doing.				
f. I felt depressed.				
g. I felt that everything that I did was an effort.				
h. I felt hopeful about the future.				
i. I thought that my life had been a failure.				
j. I felt fearful.				
k. My sleep was restless				

l. I was happy.				
m. I talked less than usual.				
n. I felt lonely.				
o. People were unfriendly.				
p. I enjoyed life.				
q. I had crying spells.				
r. I felt sad.				
s. I felt that people dislike me.				
t. I could not get "going."				

The next questions ask about what you think about your risk of developing cancer or heart disease. Give me a percent between 0 and 100%.

9. What do you believe that your chance of developing breast cancer is by age 70 if you have yearly mammograms, but choose not to have prophylactic surgery, take tamoxifen, or take HRT (Hormone Replacement Therapy) or raloxifene after menopause in a percentage? _____ %

10. ...How about if you do have a prophylactic mastectomy? _____%

11. ...How about if you do have a prophylactic oophorectomy? _____%

12. ...How about if you do take tamoxifen? _____%

13. ...How about if you do take HRT after menopause? _____%

14. ...How about if you do raloxifene after menopause? _____%

15 .What do you believe your chance of developing ovarian cancer is by age 70 if you choose not to have a prophylactic oophorectomy in a percentage? _____ _____%

16. ...How about if you do have a prophylactic oophorectomy? _____%

17. What do you believe your chance of developing heart disease by age 70 is if you choose not to take HRT or raloxifene at the onset of menopause in a percentage? _____%

18. ...How about if you do take HRT at the onset of menopause? _____%

19. ...How about if you do take raloxifene at the onset of menopause? _____%

20.The next questions are about comments made by people concerned about breast cancer (BC), and/or ovarian cancer (OC). Please tell us how frequently these comments were true for you during the past week, not at all, rarely, somewhat, or often.

During the past week:	Not at all	Rarely	Sometimes	Often
a. You thought about BC and/or OC when you didn't mean to.				
b. You had trouble falling asleep or staying asleep because of pictures or thoughts about BC and/or OC that came into your mind.				
c. You had waves of strong feelings about BC and/or OC.				
d. You had dreams about BC and/or OC.				
e. Pictures about BC and/or OC popped into your mind.				
f. Any reminder brought back feelings about BC and/or OC.				

21.Thinking about the choices that you are making please listen to the following comments some people make. Tell me whether you strongly agree, agree, neither agree nor disagree, disagree, or strongly disagree for each statement that I read to you.

	Strongly agree	Agree	Neither agree nor disagree	Disagree	Strongly disagree
a.These decisions are hard for me to make.	1	2	3	4	5
b. I'm not confident with my decisions.	1	2	3	4	5
c. It's clear which choices are best for me.	1	2	3	4	5
d. I'm aware of the management options I have to modify my risk.	1	2	3	4	5
e. I feel I know the benefits of the management options for my risk.	1	2	3	4	5
f. I am satisfied that I am adequately informed about the issues important to my decision.	1	2	3	4	5
g. I feel I know the risks and side effects of the management options for my risk.	1	2	3	4	5

h. I feel I am making an informed choice.	1	2	3	4	5
i. I am satisfied that these are my decisions to make.	1	2	3	4	5
j. I expect to successfully carry out the decisions that I am making.	1	2	3	4	5
k. I am satisfied that my decisions are consistent with my personal values.	1	2	3	4	5
l. The decisions that I am making are the best possible for me personally.	1	2	3	4	5

Appendix F
Recruitment Advertisement

BREAST CANCER RESEARCH STUDY

The University of Pennsylvania Cancer Risk Evaluation Program is looking for eligible women to take part in a breast cancer related research study. The study aims to improve the information that women **who have tested positive for either a BRCA1 or BRCA2 mutation** receive about their risk management options. If you would like to learn more about this research study please contact Nikki @ 215-573-7907.

Appendix G
Published Manuscripts

Effect of Framing as Gain versus Loss on Understanding and Hypothetical Treatment Choices: Survival and Mortality Curves

KATRINA ARMSTRONG, MD, MSc, J. SANFORD SCHWARTZ, MD, GENEVIEVE FITZGERALD, BA, MARY PUTT, ScD, PETER A. UBEL, MD

Background. *Presentation of information using survival or mortality (i.e., incidence) curves offers a potentially powerful method of communication because such curves provide information about risk over time in a relatively simple graphic format. However, the effect of framing as survival versus mortality on understanding and treatment choice is not known.* ***Methods.*** *In this study, 451 individuals awaiting jury duty at the Philadelphia City Courthouse were randomized to receive 1 of 3 questionnaires: (1) survival curves, (2) mortality curves, or (3) both survival and mortality curves. Each questionnaire included a brief description of a hypothetical treatment decision, survival curve graphs and/or mortality curve graphs presenting the outcome of the treatment, and questions measuring understanding of the information contained in the graphs and preference for undergoing treatment. After completing a brief practice exercise, participants were asked to answer questions assessing their ability to interpret single points on a curve and the difference between curves, and then to decide whether they would choose to undergo preventive surgery for 3 different scenarios in which the benefit of surgery varied.* ***Results.*** *Participants who received only survival curves or who received both survival and mortality curves were significantly more accurate in answering questions about the information than participants who received only mortality curves ($P < 0.05$). For 2 of the 3 treatment presentations, participants who received only mortality curves were significantly less likely to prefer preventive surgery than participants who received survival curves only or both survival and mortality curves ($P < 0.05$). The effect of framing on understanding was greatest among participants with less than a college education and among non-Caucasian participants.* ***Conclusion.*** *Framing graphic risk information as chance of death over time results in lower levels of understanding and less interest in preventive surgery than framing as chance of survival over time.* ***Key words:*** *Decision making; framing effect; risk communication.* ***(Med Decis Making 2002;22:76–83)***

Survival curves are a potentially powerful tool to communicate information about the outcomes of alternative choices.[1] Because survival curves provide a graphic presentation of the risk of an outcome over time, they include a large amount of information that is difficult to convey with numbers alone.[2,3] Furthermore, use of survival curves avoids the problem of having to select which time points to present—a selection that has been shown to influence choice.[4]

Presentation of probabilistic information as gain versus loss has been demonstrated to influence decision making.[5–10] Patients presented with surgical mortality as a 10% chance of dying are less likely to choose surgery than patients presented with surgical mortality as a 90% chance of surviving.[5] Because of the power of this framing effect, many experts argue that information should be presented in both formats in an attempt to "unbias" the presentation.[10,11]

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Received 28 November 2000 from the Department of Medicine, University of Pennsylvania School of Medicine (KA, JSS, GF, PAU); the Leonard Davis Institute of Health Economics, University of Pennsylvania (KA, JSS, PAU); the Center for Clinical Epidemiology and Biostatistics, University of Pennsylvania School of Medicine (KA, JSS, MP, PAU); the University of Pennsylvania Cancer Center (KA, JSS, MP, PAU); and the Philadelphia Veterans Affairs Medical Center (PAU). Revision accepted for publication 17 September 2001. This work was supported by Grant No. BC971623 from the Department of the Army Breast Cancer Research Program. Dr. Armstrong is a Robert Wood Johnson Foundation Generalist Physician Faculty Scholar and supported by American Cancer Society Clinical Research Training Grant no. 99-023-01. Dr. Ubel is a Robert Wood Johnson Foundation generalist physician faculty scholar and a senior research associate in health services research from the Department of Veterans Administration. The funding agreement ensured the authors' independence in designing the study, interpreting the data, and writing and publishing the report.

Presentation of graphic information about the probability of dying over time can also be framed as a gain or a loss using survival or mortality curves. Although several other framing effects have been demonstrated with survival curves, the effect of framing information as survival curves versus mortality curves is not known.[4,12–14] Furthermore, although presentation of both gain and loss formats may reduce the bias from presenting 1 format only, it greatly increases the complexity of the presentation and may decrease understanding. Thus, the aims of our study were to determine whether framing of information as survival curves or mortality curves affects understanding of the information or the preferred alternative, and whether presenting both survival and mortality curves reduces framing effects.

Methods

DESIGN

We conducted an experiment that compared the effects of presenting the same information about the outcomes of a hypothetical medical decision as (1) probability of surviving over time (survival curves), (2) probability of dying over time (mortality curves), or (3) probability of surviving and probability of dying (survival and mortality curves). Outcomes included understanding of the information and treatment preference and were measured using questions that were consistent with the format of the curves (i.e., questions about mortality curves asked the number of people who had died and questions about survival curves asked the number of people still alive). The study protocol was approved by the Human Subjects Committee of the Institutional Review Board at the University of Pennsylvania.

SETTING AND PARTICIPANTS

Prospective jurors awaiting jury selection at the Philadelphia City Courthouse were offered a candy bar to complete a study questionnaire. When all prospective jurors were assembled in a single room, a research assistant made an announcement about the survey and randomly distributed questionnaires to volunteers. Based on our experience with this method, we estimate that approximately 75% of prospective jurors volunteer to participate and more than 90% of individuals who volunteer complete the questionnaires. In Philadelphia, individuals are randomly selected for jury duty from voter registration and drivers license records.

INTERVENTION

Three versions of a questionnaire were developed: survival curves only, mortality curves only, and survival and mortality curves. For each version, care was taken to ensure that the presentation of information throughout the questionnaire was consistent with the framing selected. Versions were randomly distributed to study participants.

Each questionnaire began with a brief explanation of survival and/or mortality curves and a graph showing a single curve with 4 questions asking the number of people alive at different points in time. The explanation of survival curves read as follows:

> A survival curve is a picture that shows how long people live after being diagnosed with or treated for a disease. Survival curves are shown to patients to help them understand their disease and to decide which treatment option is best for them.

After the graph containing a single survival curve, the explanation continued:

> The above graph is a survival curve. It shows the number of people who survive after being diagnosed with an imaginary condition, Chocolitis. It begins in the upper left-hand corner with 100 patients diagnosed at year 0. The graph shows how many people are alive every 5 years after being diagnosed.

The explanation of mortality curves read as follows:

> A mortality curve shows the number of people who die after being diagnosed with or treated for a disease. These graphs are shown to patients to help them understand their disease and to decide which treatment option is best for them.

After the graph containing a single mortality curve, the explanation continued:

> The above graph is a mortality curve. It shows the number of people who die after being diagnosed with an imaginary condition, Soapoperitis. It begins in the lower left-hand corner with 100 patients diagnosed at year 0. The graph shows how many people died every 5 years after being diagnosed.

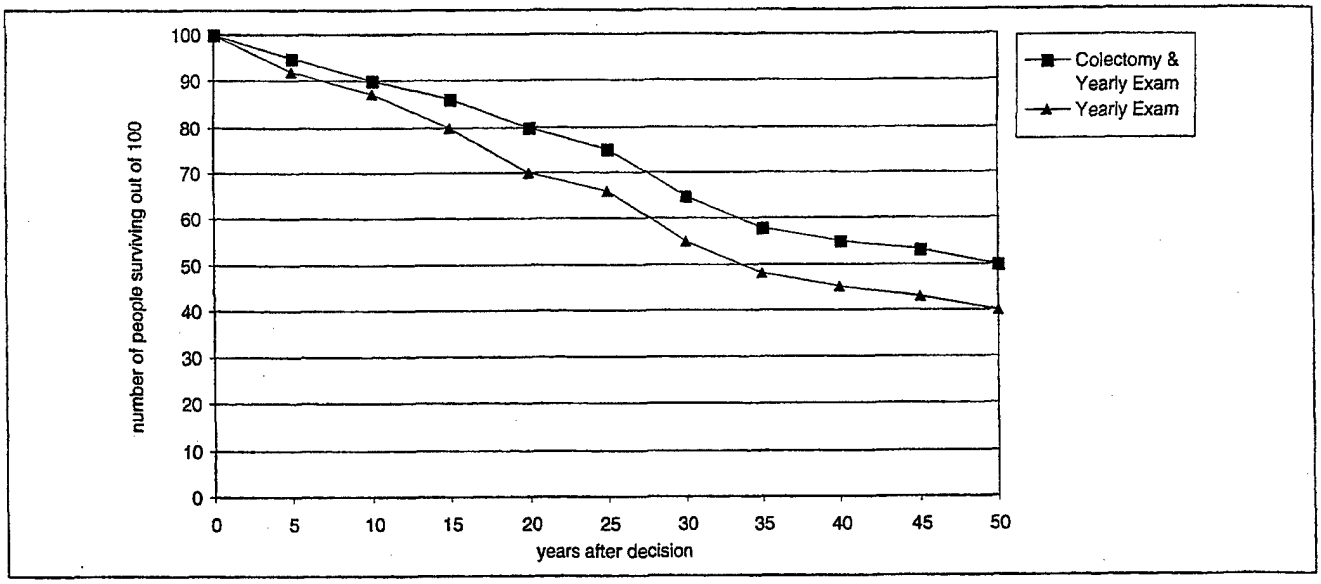

Figure 1. Survival curve graph.

We found this single-curve introduction improved understanding of graphs with 2 survival curves in a previous study. The questionnaire then presented a hypothetical scenario requiring a decision about a preventive treatment, graph(s) containing curves illustrating the chance of survival/death after the 2 possible choices, and outcome measurement questions. The hypothetical scenario read as follows:

> Imagine you are at increased risk of developing colon cancer. Yearly exams with a physician are recommended for everyone at increased risk for colon cancer. In addition to a yearly exam, you can choose to have a colectomy (removal of part of your colon) along with a colostomy (a plastic bag attached to your abdomen into which you empty your bowels). This procedure results in a lowered risk of developing colon cancer. The graph(s) on the facing page shows what we would expect to happen to 100 people just like you if they chose to have a colectomy with a colostomy or to have no surgery.

For each version of the questionnaire, the same size graph or graphs were presented on the left-hand page of a booklet with questions about the graph(s) on the right-hand page. For the questionnaire presenting both survival and mortality curves, survival curves were shown on the top graph and mortality curves on the bottom graph with an explanation that both graphs showed the same information about what was expected to happen. Figure 1 shows the survival curve graph, and Figure 2 shows the mortality curve graph.

OUTCOME MEASURES

We measured understanding by asking participants to interpret the number of people alive (or dead) at a point in time on a given curve (e.g., "How many people who have a colectomy are alive at year 20?"), determine which choice results in more people alive (or dead) at a point in time (e.g., "In which group are more people alive at year 30?"), and calculate the difference in the number of people alive (or dead) between curves at a point in time (e.g., "How many more people are alive in this group at year 10?"). The framing of the questions (alive vs. dead) mirrored the framing of the curves. For the questionnaire presenting both survival and mortality curves, an explanation was provided about the relationship between the number of people alive (based on the survival curve) and the number of people dead (based on the mortality curve) at any point in time. We measured treatment and preference by asking participants to decide whether they would want to have a preventive colectomy (i.e., "Given this information, which option would you choose?"). To determine whether framing as survival versus mortality affected the transitivity of preferences, we asked about preference for surgery at 3 levels of benefit of colectomy, each shown by a separate graph with 2 curves. We refer to these 3 levels of benefit by the proportional increase in absolute survival (5%, 10%, or 20% at 50 years) in this article. These relative percentages were not included on the graphs. For all questionnaires, the 10% gain in survival was presented first, followed by the 5% gain and then the 20% gain.

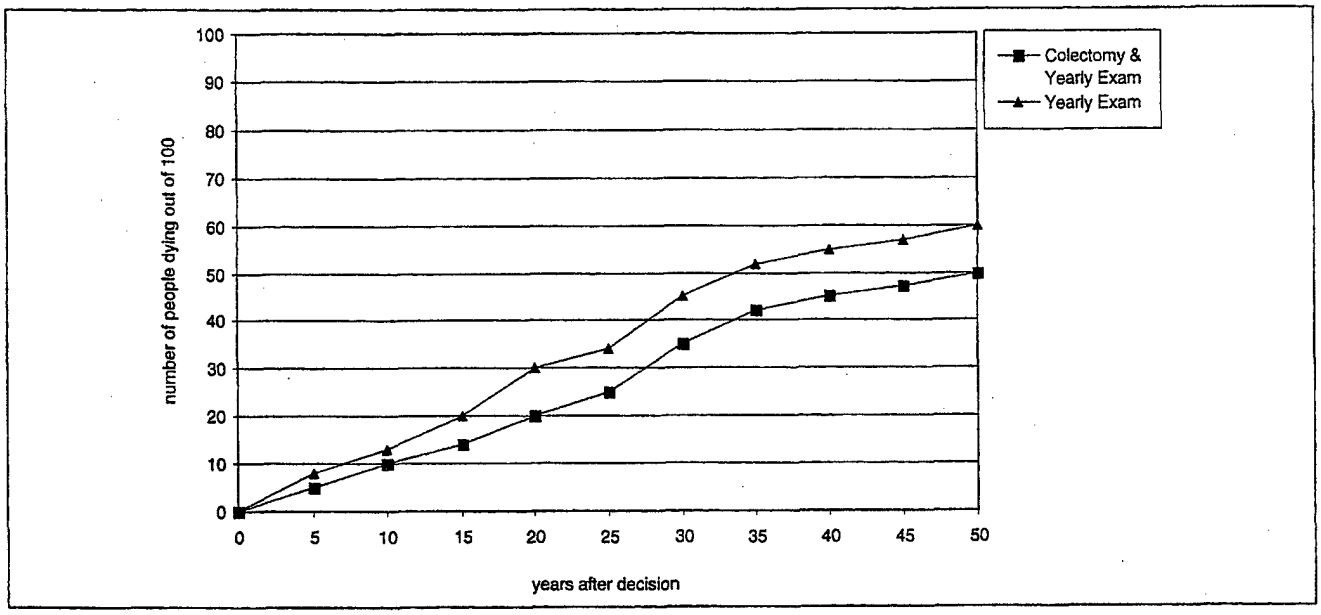

Figure 2. Mortality curve graph.

STATISTICAL ANALYSIS

Baseline characteristics of the 3 groups were compared using chi-square tests for categorical variables and analysis of variance followed by pairwise *t* tests for continuous variables. Three types of accuracy were measured: (1) interpretation of number of people alive or dead in a single group at a point in time, (2) determination of which group had more alive or dead at a point in time, and (3) calculation of the difference in number of people alive or dead between groups at a point in time. Two questions were included for each type. Participants were categorized as accurate if they answered both questions correctly, partially accurate if they answered 1 of the 2 questions correctly, and inaccurate if they answered neither question correctly. For the purposes of these analyses, these categories were dichotomized into accurate and not accurate (which included both partially accurate and inaccurate). Chi-square tests were used to compare the proportion of people who answered accurately and the proportion of participants who preferred surgery at each level of benefit between groups.

Multivariate analyses were conducted to assess the impact of gender, race, education, and age on the effect of framing on understanding and choice and the impact of understanding on choice. For these analyses, a single composite understanding variable was created that was coded 1 if participants answered all of the understanding questions correctly and 0 if they had any incorrect answers. Separate logistic regression models were constructed with understanding as the dependent variable and with preference as the dependent variable. The independent variables in the understanding model were frame, age, gender, education (high school vs. more than high school), and race (Caucasian vs. non-Caucasian). The independent variables in the preference model were frame, understanding, age, gender, education (high school vs. more than high school), and race (Caucasian vs. non-Caucasian). Variables were kept in the model if they were significantly associated with the dependent variable according to a Wald test ($P < 0.05$) or altered the coefficient for another variable by more than 15%. In addition, for each model, interaction terms were tested for potential interactions between the information frame (survival, mortality, or both) and demographic characteristics. Likelihood ratio tests were used to determine whether the interaction terms were significant. For interaction terms that were significant according to the likelihood ratio tests, Wald tests were used to identify the specific source of the interaction. Subsequent secondary analyses were conducted with level of understanding as a continuous variable (i.e., proportion of understanding questions answered correctly). However, because the conclusions of these analyses were the same as when understanding was analyzed as a categorical variable, we present only the categorical analyses. All *P* values are 2-sided.

Table 1 Subject Characteristics

	Mortality Curve	Both Curves	Survival Curve
Mean age (range)	42.9 (18-79)	42.6 (20-76)	41.2 (20-72)
Female	70%	65%	72%
Caucasian	52%	55%	46%
African American	40%	38%	45%
Mean years of education (range)	13.7 (8-17)	14.1 (9-19)	13.4 (8-17)

Results

We recruited a total of 451 participants, of whom 150 received the survival curve format, 151 received the mortality curve format, and 150 received the survival and mortality curve format. The 3 groups were not statistically different in age, gender, education, and ethnicity ($P > 0.6$) (Table 1).

EFFECT OF FRAMING ON UNDERSTANDING

Participants who received the information framed as survival curves or survival and mortality curves were more likely to accurately answer questions about the information than participants who received the information framed as mortality curves. This effect was seen for the ability (1) to interpret the number of people alive (or dead) in each treatment group at a point in time, (2) to determine which choice resulted in more people alive at a point in time, and (3) to calculate the difference in the number of people alive between groups at a point in time (Table 2). However, the impact of framing differed substantially between Caucasian and non-Caucasian ($P = 0.0004$ for test of interaction) and between subjects with more or less than a high school education ($P = 0.002$ for test of interaction) (Tables 3 and 4). For example, for Caucasians, the difference in the proportion of respondents answering correctly between the survival and mortality frames was only 6%, whereas for non-Caucasians the difference between the 2 frames was 26%. Similarly, for participants with more than a high school education, the difference in the proportion of respondents answering correctly between the survival and mortality frames was only 7%, whereas for participants with less than a high school education the difference between the 2 frames was 27%. We present results on the combined effects of education and ethnicity in Table 5. Although education and ethnicity were correlated in our study population, education and ethnicity also have independent effects on the impact of framing on understanding, with the greatest impact of framing among participants who had less than a college education and were non-Caucasian. After adjusting for age, gender, education, and ethnicity, the interactions between ethnicity and framing and between education and framing remained statistically significant ($P = 0.04$ and $P = 0.007$, respectively). Because our study was not powered to examine framing effects within the subgroups identified in Table 5, we did not test for framing effects within each subgroup. The impact of framing did not differ by gender or age of participants ($P > 0.6$).

EFFECT OF FRAMING ON CHOICE

Participants who received the information framed only as survival curves were more likely to choose to undergo preventive surgery than participants who received the information framed as mortality curves only (Table 2). Participants who received the information framed as both survival and mortality curves were less likely to choose preventive surgery than participants

Table 2 Effect of Framing on Understanding and Treatment Preference

	Mortality Curve	Both Curves	Survival Curve	*P* Value for Trend
Proportion of participants answering accurately				
Number alive (dead) in 1 group	0.54[a]	0.67[b]	0.69[b]	0.01
Which group has more alive (dead)	0.75[a]	0.84[a,b]	0.85[b]	0.05
Difference in number alive (dead) between groups	0.43[a]	0.49[a,b]	0.56[b]	0.03
All understanding questions	0.38[a]	0.48[a,b]	0.52[b]	0.02
Proportion of participants choosing colectomy				
5% increase in survival	0.39[a]	0.51[b]	0.55[b]	0.02
10% increase in survival	0.51[a]	0.56[a]	0.59[a]	0.35
20% increase in survival	0.53[a]	0.62[a,b]	0.70[b]	0.06

Note: Cells within a row that share a superscript are not statistically different at $P = 0.05$.

Table 3 Effect of Framing on Understanding According to Ethnicity

	Proportion of Participants Answering Accurately		
	Mortality	Both	Survival
Overall	0.38[a]	0.48[a,b]	0.52[b]
Caucasian ($n = 213$)	0.63[a]	0.70[a]	0.57[a]
Non-Caucasian ($n = 213$)	0.14[a]	0.34[b]	0.40[b]

Table 4 Effect of Framing on Understanding According to Education

	Proportion of Participants Answering Accurately		
	Mortality	Both	Survival
Overall	0.38[a]	0.48[a,b]	0.52[b]
More than high school ($n = 251$)	0.64[a]	0.62[a]	0.57[a]
High school or less ($n = 180$)	0.09[a]	0.35[b]	0.36[b]

Note: Cells within a row that share a superscript are not statistically different at $P = 0.05$.

receiving survival curves only and more likely to choose preventive surgery than participants receiving mortality curves only. This pattern was consistent across the 3 levels of benefit tested. However, the test for trend was only significant at $P < 0.05$ for the scenario in which colectomy increased survival by 5%. Overall, subject preferences were transitively ordered for all 3 ways of framing the information, with a greater proportion of participants choosing preventive surgery as the benefit of the surgery increased.

The effect of framing on preference for surgery was not modified by the participants' ethnicity (Caucasian vs. non-Caucasian), education, gender, or age. For the graph in which colectomy provided a 10% increase in survival, there was a trend toward a greater effect of framing on preference among individuals who answered all the understanding questions correctly (interaction $P = 0.13$). However, this trend was not seen in the graphs where colectomy provided a 5% or 20% increase in survival (interaction $P > 0.5$).

Discussion

The results of this study suggest that framing of information about risk over time as survival versus mortality curves can affect understanding and treatment preferences. Presenting information as mortality curves resulted in lower levels of understanding and fewer participants' choosing preventive colectomy than presenting information as survival curves. Presenting information in both frames (i.e., showing both survival and mortality curves) resulted in levels of understanding and preference for preventive colectomy between presentation of survival curves only and presentation of mortality curves only, but was not statistically different from presenting information as survival curves only.

The impact of gain versus loss framing on choice is most often associated with prospect theory. However, prospect theory was developed primarily to explain choices between risky and riskless options. Typically, in such risky choice framing effects, people prefer risky options when choices are negatively framed and certain outcomes when they are positively framed. Levin et al.[15] distinguished this type of framing effect from 2 others: attribute framing and goal framing. In attribute framing, people are not asked to choose between independent options; instead, they are asked to evaluate a single item. Their evaluation depends on whether a specific attribute of that item is positively or negatively framed. For example, people's attitudes toward the quality of ground beef depend on whether the beef is labeled as 75% lean or 25% fat. In goal framing, people are asked to pursue a specific goal, with the importance of the goal framed either as the positive consequences

Table 5 Effect of Framing on Understanding According to Ethnicity and Education

	Proportion of Participants Answering Accurately		
	Mortality	Both	Survival
Overall	0.38	0.48	0.52
Caucasian, more than high school ($n = 141$)	0.80	0.77	0.66
Caucasian, less than high school ($n = 72$)	0.23	0.56	0.44
Non-Caucasian, more than high school ($n = 106$)	0.32	0.44	0.50
Non-Caucasian, less than high school ($n = 107$)	0.02	0.15	0.30

of performing the act or the negative conse-quences of not performing the act. For example, women were more apt to engage in breast self-examination when presented with information stressing the negative consequences of not engaging in such examinations than when presented with information stressing the positive consequences of engaging in such examinations. Across all 3 of these framing effects, people's choices or evaluations have been shown to vary depending on whether the situation is positively or negatively framed. However, the effect of the framing manipulation on choice and evaluation depends on which of the 3 framing effects is at play.

The survival and mortality curves in our study are not clear examples of any of these types of framing effects. Unlike risky choice framing effects, neither of our options was riskless. Unlike attribute framing, we did not ask people to make mere evaluations; rather, we asked them to choose between 2 options. Unlike goal framing, we did not ask people to pursue some goal; rather, we asked them to make a choice. In fact, survival and mortality curves represent an interesting new context in which to study framing effects. They have unique features that deserve to be studied. For example, survival curves present the number of people alive at any point in time. This is a positive way of framing the information. But survival curves represent this number graphically as a loss, that is, a decrease from 100% survival. Similarly, mortality curves present the number of people dead at any given time, a negative framing. However, they represent this number graphically as a gain, that is, an increase from 0% mortality.

The complexity of the framing effect created by survival curves is better illustrated by comparing it to simpler ways of presenting people with medical choices. Suppose, for example, people are asked to decide whether they want to undergo a surgery that has a 95% survival rate. Consistent with attribute framing effects that have been found, it would be expected that they would view this surgery more positively than a surgery they were told had a 5% mortality rate. This type of framing effect is quite predictable and relatively well understood. By contrast, in our study, we presented people with 2 curves, illustrating survival (or mortality) rates for surgery versus no surgery. Presenting this information in terms of survival curves potentially makes both surgery and going without surgery more attractive because both options would be described in terms of the number of people surviving. It is not at all clear how this framing of the information would change the relative desirability of the 2 options. Similarly, when looking at survival curves of these 2 options, people might focus on how many more patients are alive who underwent surgery. By contrast, with mortality curves, people might focus on how many more patients are dead who did not receive surgery.

There is another reason that the framing effects created by survival and mortality curves in this study are difficult to categorize: The psychophysical space between the 2 treatment options differs across the 2 types of curves. Consider the outcomes 50 years after the decision. In the survival curve, surgery increases absolute survival from 40% to 50%, a relative gain of 25%. In the mortality curves, it reduces mortality from 60% to 50%, a 16.7% relative reduction. Future research should focus on trying to tease apart what people attend to when viewing survival or mortality curves.

Most studies of the impact of gain versus loss framing have used information about outcomes at a single point in time (e.g., risk of death with treatment A vs. risk of survival with treatment A).[5–7,9,16,17] These studies have been unable to examine the effect of framing on understanding beyond the ability to repeat the single piece of risk information provided. Because survival and mortality curves contain extensive information about risk over time, they allowed us to assess the impact of gain versus loss framing on more wide-ranging measures of understanding. In this study, presentation of information as mortality curves resulted in significantly lower levels of understanding (as measured by answers to questions about the information) than presentation of information as survival curves. This framing effect appeared to be greatest among individuals with less education or minority race. Although the reason for this difference is not clear from the current study, it is interesting to speculate that the greater difficulty in answering questions about loss may suggest that participants are more averse to thinking in terms of loss, more confused by mortality curves because a rise in the curve signifies a greater loss (i.e., more people dying), or more familiar with the term "survival" than the term "mortality." Furthermore, these factors may be more common among less educated participants, explaining the interaction with educational level. Practically, however, this finding suggests that care must be taken in assuming that information framed as gain or loss is equally well understood among subjects from different backgrounds. Framing information as a loss may result in both less interest in an intervention and lower levels of understanding.

Although presentation of both gain and loss framing is often proposed as the best way to resolve the bias created by presentation using either frame alone, our study provides some of the first empirical evidence about the outcomes of such a strategy.[10,11] In this study, presentation of both survival and mortality curves re-

sulted in preferences and understanding in between those seen with the presentation of either frame alone, although not statistically different from preferences with survival curves only. Further studies with greater power to measure relatively small differences in preference between groups are needed to determine whether the trend toward the use of both frames to unbias the presentation seen in this study represents a real effect.

This study has several limitations. Although the juror pool is highly representative of the population of the city of Philadelphia, it is less representative of other segments of the U.S. population. We chose to use jurors rather than patients because of concerns about patients misinterpreting the data from the hypothetical situations as reflections of their own health status. Because of the nature of our experimental study design, we were able to compare only 3 alternative formats of our questionnaire. Clearly, the format of each part of the questionnaire from the introduction to the outcome questions may affect the results. Our results are not necessarily generalizable to other formats.

Involving patients in medical decisions requires effective communication of information about the risks and benefits of alternative choices. Presentation of information using survival or mortality (i.e., incidence) curves offers a potentially powerful method of communication in this setting because such curves provide extensive information about risk over time in a relatively simple graphic format. However, presentation of either survival or mortality curves alone can result in an effect of framing on understanding and treatment preference.

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BRIEF REPORT

Using Survival Curve Comparisons to Inform Patient Decision Making

Can a Practice Exercise Improve Understanding?

Katrina Armstrong, MD, MSc, Genevieve FitzGerald, BA, J. Sanford Schwartz, MD, Peter A. Ubel, MD

BACKGROUND: **Patients often face medical decisions that involve outcomes that occur and change over time. Survival curves are a promising communication tool for patient decision support because they present information about the probability of an outcome over time in a simple graphic format. However, previous studies of survival curves did not measure comprehension, used face-to-face explanations, and focused on a VA population.**

METHODS: **In this study, 246 individuals awaiting jury duty at the Philadelphia County Courthouse were randomized to receive one of two questionnaires. The control group received a questionnaire describing two hypothetical treatments and a graph with two survival curves showing the outcomes of each treatment. The practice group received the same questionnaire preceded by a practice exercise asking questions about a graph containing a single curve. Subjects' ability to interpret survival from a curve and ability to calculate change in survival over time were measured.**

RESULTS: **Understanding of survival at a single point in time from a graph containing two survival curves was high overall, and was improved by the use of a single curve practice exercise. With a practice exercise, subjects were over 80% accurate in interpreting survival at a single point in time. Understanding of changes in survival over time was lower overall, and was not improved by the use of a practice exercise. With or without a practice exercise, subjects were only 55% accurate in calculating changes in survival.**

CONCLUSION: **The majority of the general public can interpret survival at a point in time from self-administered survival curves. This understanding is improved by a single curve practice exercise. However, a significant proportion of the general public cannot calculate change in survival over time. Further research is necessary to determine the effectiveness of survival curves in improving risk communication and patient decision making.**

KEY WORDS: **decision making; communication; patient education.**

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Patients often face medical decisions involving outcomes that occur and change over time. Choosing an aggressive treatment over a less aggressive treatment may trade short-term increase in mortality for long-term increase in survival. In many situations, a patient must understand both the conditional probabilities of an outcome and how those probabilities change over time. Although it is well established that patients want to receive risk information, how best to present this complex information is not clear.[1] Extensive numerical information may overwhelm a patient's ability to process and understand it.[2,3] However, presenting limited information, for example, survival probabilities at two or three time points, may bias decisions.[4,5]

Survival curves may overcome these problems by presenting information about the probability of an outcome over time in a simple graphic format without extensive numeric data. Several studies have used survival curves to convey information about treatment choices to patients in face-to-face discussions.[6–9] We have chosen to extend this research for several reasons. First, recent literature suggests patients may have difficulty understanding even simple probabilities.[10] Prior studies did not measure subjects' ability to understand survival curve information. Second, because many decision aids being developed are self-administered, it is important to establish whether patients can understand self-administered survival curves.[11,12] Finally, participants for prior studies came from Veterans' Administration (VA) clinics and may not be generalizable to other patient populations.

Using survival curves to aid decision making involves making comparisons between multiple curves. Although a survival curve is a relatively simple method of presenting complex information, a graph containing multiple survival curves may appear sufficiently complex to be overwhelming. The ability to perform many cognitive tasks is dependent on the development of cognitive rules or heuristics.[3,13] For survival curve understanding, we hypothesized that these rules would be more easily developed on a relatively more simple graph containing a single curve, and, thus, presenting individuals with a graph containing a single curve prior

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to a graph containing multiple curves would improve understanding of the more complex, multiple curve graph.

The objectives of our study were to determine: 1) if the general public can understand survival curves when presented in a self-administered format; and 2) if understanding of a graph containing a two-curve comparison improves with a single curve practice exercise.

METHODS

Study Design

We randomized study subjects to receive one of two questionnaires. The control group received a questionnaire describing a hypothetical health condition with two possible treatments and a graph with two survival curves showing the outcomes of the treatments. The practice group received the same questionnaire preceded by a practice exercise asking questions about a graph containing a single curve. The study protocol was approved by the Human Subjects Committee of the Institutional Review Board at the University of Pennsylvania.

Study Setting and Participants

Prospective jurors awaiting jury selection at the Philadelphia County Courthouse were offered a candy bar to complete the study questionnaire. The two versions of the questionnaire were randomly ordered and distributed sequentially to volunteers. Based on our prior experience, we estimated that approximately 75% of prospective jurors volunteer to participate and over 90% of individuals who volunteer complete the questionnaires. In Philadelphia, individuals are randomly selected for jury duty from voter registration and drivers license records.

Intervention

Each participant received a self-administered questionnaire that included a brief explanation of survival curves and a graph containing two survival curves illustrating the outcomes of two hypothetical treatments and outcome measurement questions (see below) (Appendix A). The brief explanation read:

> *We will show you a graph of survival curves. A survival curve is a picture that shows how long people live after being diagnosed with a disease. You will notice there are different curves on the graph. Each curve shows how many people survive using the different treatments for a disease. Survival curves are shown to patients to help them understand their disease and to decide which treatment option is best for them.*

A brief explanation of the graph was provided below the two curve graph:

> *The graph above shows how many people survive after either having surgery or being put on medication for an imaginary disease called Soap-operatitis. At year 0, 100 patients were started on Soap-operatitis medication and 100 patients had Soap-operatitis surgery. The curve marked by the squares shows the patients who had surgery. The curve marked by the circles shows the patients who are on medication. The curves show how many people are alive every five years after having surgery or being put on medication.*

For participants randomized to the practice arm, the questionnaire began with an additional page containing a practice exercise with a single survival curve for a hypothetical condition and several questions about the information contained in the curve (Appendix B). The correct answers to these questions were not provided.

Outcome Measures

The primary outcome measure was comprehension of the information contained in the figure containing two survival curves. Subjects both interpreted survival rates at a single time point (e.g., How many people having surgery are alive at year 20?) and change in survival over a specific time period (e.g., How many people having surgery died between year 20 and year 40?). Answers were considered correct only if they exactly matched the correct answer. Answers left blank were considered missing data, rather than incorrect answers.

Statistical Analysis

Baseline characteristics of the two groups were compared using χ^2 tests for categorical variables and t tests for continuous variables. For each subject, separate accuracy scores were generated for the ability to interpret the number alive at a given point (five questions) and the ability to calculate change in survival (two questions), by dividing the number of questions answered correctly by the total number of questions. Because these scores were not normally distributed, they were compared between groups using the Mann-Whitney U test. For the practice group, accuracy scores were generated for the single curve graph and compared within subject to their accuracy scores for the double curve graph using the Wilcoxon signed rank test.

RESULTS

Of the 246 subjects who completed the questionnaire, 120 received the practice intervention and 126 did not. The two groups were similar in age, gender, education, and ethnicity (Table 1).

Table 1. Subject Characteristics

	Practice Exercise	Control	*P* Value
Mean age (±SD)	39.7(12.4)	39.9(12.7)	.88
Women, %	68	66	.82
Caucasian, %	55	47	.24
African American, %	40	44	.12
Mean years of education (range ± SD)	13.8(2.2)	14.0(2.2)	.78

Table 2. Comprehension of Double Curve Presentation

	Practice Exercise	Control	*P* Value
% Correctly identifying number of survivors at a single point	83	74	.03
% Correctly identifying change in number of survivors between two time points	55	55	.89

Understanding of survival at a single point in time from a graph containing two survival curves was high overall and improved with a single curve practice exercise (Table 2). With a practice exercise, subjects were over eighty percent accurate in interpreting survival at a single point in time. Furthermore, two thirds of subjects (66%) answered all of these questions correctly and an additional 14% answered all but one question correctly. Understanding of changes in survival over time was lower overall, and was not improved by the use of a practice exercise (Table 2). With or without a practice exercise, subjects were only 55% accurate in calculating change in survival. Furthermore, only 54% of subjects answered over half of these questions correctly, and 33% were unable to answer any question correctly. Mean accuracy scores did not differ significantly by gender, educational level, or ethnicity (all $P > .10$).

Among individuals receiving a single curve practice exercise, understanding of the graph containing a single curve was greater than understanding of the graph containing two curves. The great majority of errors in interpreting survival or calculating change in survival were large in magnitude. For example, accuracy in interpreting the number of people alive at a point in time declined from 92% in the single curve graph to 83% in the double curve graph ($P = .006$), and accuracy in calculating change in survival over time declined from 67% to 55% ($P = .04$).

DISCUSSION

Our results suggest that the majority of the general public can understand survival at a point in time from a graph comparing two survival curves and that this understanding is improved by a single curve practice exercise. However, almost half of our subjects could not calculate a change in survival over time from a survival curve—a task that requires subjects to correctly estimate the number of people surviving at two time points and to accurately subtract those two numbers.

Prior studies have used survival curves to demonstrate that patients focus on different portions of survival curves than physicians, that order of presentation affects treatment preferences, that length of the explanation affects treatment preferences and that patients are willing to trade a short term increase in mortality for long term increase in survival.[5–8] To our knowledge, our study is the first to demonstrate that the general public can calculate survival from a survival curve even without a face-to-face explanation. Importantly, however, our study raises significant concerns about the ability of the general public to calculate differences in survival from a survival curve. Such comparisons may be an important component of the cognitive tasks necessary for patients to use survival curve information to aid their decision making.

Our study has several limitations. Although the juror pool is highly representative of the Philadelphia population, it is less representative of other segments of the U.S. population. Second, we compared only two formats of our questionnaire. The format of each part of the questionnaire may affect the results. Our results are not necessarily generalizable to other formats. Third, because the instructions on the questionnaire were written at a ninth-grade reading level and in relatively small font, it is possible that they were not understood by some participants.

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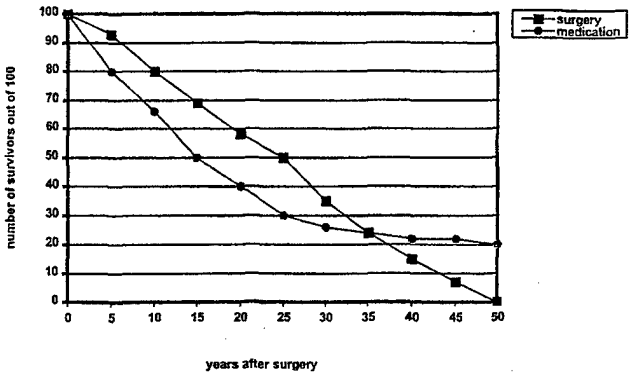
APPENDIX A

Double Curve Graph

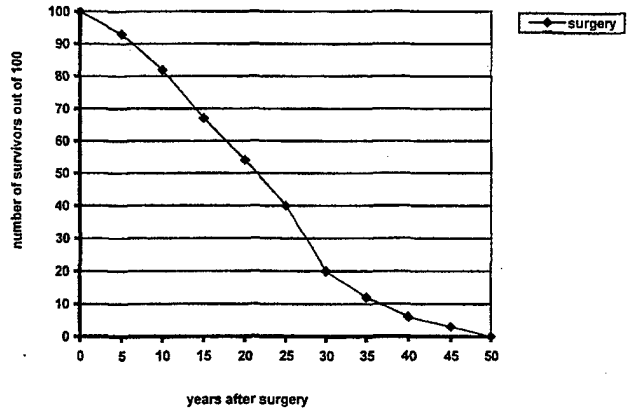


The graph above shows how many people survive after either having surgery or being put on medication for an imaginary disease called Soap-operatitis. At year 0, 100 patients were started on Soap-operatitis medication and 100 patients had Soap-operatitis surgery. The curve marked by the squares shows the patients who had surgery. The curve marked by the circles shows the patients who are on medication. The graphs show how many people are alive every five years after having surgery or being put on medication.

1. How many people are alive at year 0 who are on medication? _____
2. How many people are alive at year 0 who have surgery? _____
3. How many people are alive at year 15 after receiving medication? _____
4. How many people are alive at year 20 after having surgery? _____
5. How many people are alive at year 25 after having surgery? _____
6. How many people on medication died between years 5 and 15? _____
7. How many people died after having surgery between years 20 and 25? _____
8. Which treatment would you choose? _____

APPENDIX B

Single Curve Practice Exercise



The above graph shows the number of people who survive after having surgery for a disease called Chocalitis. It begins with 100 patients having surgery at year 0. The graph shows how many people are alive every five years after having surgery. For example, twenty years after surgery, 54 people are still alive. Please answer the following questions using the above graph.

1. How many people are alive at year 0? _____
2. How many people are alive at year 25? _____
3. How many people died between year 0 and year 30? _____
4. How many people are alive at year 50? _____
5. Did more people die between years 0 and 5 or between years 10 and 15? _____

Cost-Effectiveness of Raloxifene and Hormone Replacement Therapy in Postmenopausal Women: Impact of Breast Cancer Risk

Katrina Armstrong, MD, MSc, Tze-Ming Chen, MD, Daniel Albert, MD, Thomas C. Randall, MD, and J. Sanford Schwartz, MD

OBJECTIVE: To examine the life expectancy and cost-effectiveness of hormone replacement therapy (HRT) and raloxifene therapy in healthy 50-year-old postmenopausal women.

METHODS: We performed a cost-effectiveness analysis using a Markov model, discounting the value of future costs and benefits to account for their time of occurrence.

RESULTS: Both HRT and raloxifene therapy increase life expectancy and are cost-effective relative to no therapy for 50-year-old postmenopausal women. For women at average breast cancer and coronary heart disease risk, lifetime HRT increases quality-adjusted life expectancy more (1.75 versus 1.32 quality-adjusted life years) and costs less ($3802 versus $12,968) than lifetime raloxifene therapy. However, raloxifene is more cost-effective than HRT for women at average coronary risk who have a lifetime breast cancer risk of 15% or higher or who receive 10 years or less of postmenopausal therapy. Raloxifene is also the more cost-effective alternative if HRT reduces coronary heart disease risk by less than 20%.

CONCLUSIONS: Assuming the benefit of HRT in coronary heart disease prevention from observational studies, long-term HRT is the most cost-effective alternative for women at average breast cancer and coronary heart disease risk seeking to extend their quality-adjusted life expectancy after menopause. However, raloxifene is the more cost-effective alternative for women at average coronary risk with one or more major breast cancer risk factors (first-degree relative, prior breast biopsy, atypical hyperplasia or *BRCA1/2* mutation). These results can help inform decisions about postmenopausal therapy until the results of large scale randomized trials of these therapies become available. (Obstet Gynecol 2001;98:996–1003. © 2001 by the American College of Obstetricians and Gynecologists.)

Deciding about the use of hormone replacement therapy (HRT) or raloxifene after menopause is difficult. These therapies have multiple, often competing effects.[1–7] The most effective method of extending life expectancy depends upon an individual woman's risk for osteoporotic fracture, coronary heart disease, or breast cancer, and the relative efficacy of these therapies on reducing these events. Synthesizing this complex information is made particularly difficult by the large number of often conflicting studies and the need to extrapolate the efficacy of raloxifene on clinical outcomes from surrogate endpoints and the efficacy of HRT from observational studies.[5,6,8] Furthermore, differences in prescription drug costs of raloxifene therapy and HRT suggest that the short- and long-term economic costs of these therapies may vary substantially.

In this setting, decision analysis offers a systematic approach to evaluating the comparative clinical and cost-effectiveness of alternative therapies, including the impact of alternative assumptions on outcomes of interest. The objective of the present study was to examine the life expectancy and cost-effectiveness of HRT and raloxifene therapy to prevent the long-term complications of estrogen deficiency among healthy postmenopausal women.

MATERIALS AND METHODS

Clinical and cost-effectiveness were estimated using a time-dependent Markov model that simulated the out-

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Table 1. Disease Incidence and Mortality

		Sensitivity analysis range	Source(s) (references)
Coronary heart disease			
Incidence	0.32 lifetime	0.30–0.90	11, 12
Mortality	0.1–0.3 first y	0.05–0.4	14, 15
	0.01–0.04 subsequent y	0.005–0.02	
Hip fracture			
Incidence	0.14 lifetime	0.10–0.40	25
Mortality	0.17 first y	0.08–0.35	26
Vertebral fracture			
Incidence	0.18 lifetime	0.04–0.20	27
Mortality			
Breast cancer			
Incidence	0.10 lifetime	0.05–0.50	28
Mortality	0.025 first y	0.01–0.05	28
	0.032 subsequent y	0.01–0.05	
Endometrial cancer			
Incidence	0.026 lifetime	0.01–0.05	28
Mortality	0.15 first y	0.05–0.3	28
Thromboembolism			
Incidence	0.00072 annually	0.0003–0.002	4
Mortality	0.016 first y	0.008–0.03	29

comes of HRT, raloxifene, or no therapy in hypothetical cohorts of 50-year-old healthy postmenopausal women. The simulation included the six major outcomes affected by raloxifene and HRT: coronary heart disease, vertebral fracture, hip fracture, thromboembolism, endometrial cancer, and breast cancer. Because data about the impact of HRT on colon cancer and Alzheimer's disease are preliminary and corresponding data are not available for raloxifene, these outcomes were not included in the simulation. Risks of developing each outcome were independent of prior outcomes. The simulation was run until all cohort members died or reached age 101.

The analysis compared three alternative regimens: HRT (0.625 mg of oral conjugated estrogen per day with cyclic progestin for 10–14 days per month in women with an intact uterus); raloxifene (60 mg per day); and no treatment. All women were assumed to be compliant with therapy. The base-case analysis examined use of continuous therapy from age 50 until death. Because some women take HRT or raloxifene for shorter time periods, therapy of 5- and 10-years duration after menopause at age 50 was examined in secondary analyses, with benefits of therapy assumed to continue only while therapy was used.

Simulation outcomes included life expectancy, quality-adjusted life years, and direct medical cost.[9] Although the inclusion of all direct medical costs is consistent with a societal perspective, nonhealth effects, health effects on people other than the woman in question, indirect medical costs and nonmedical costs are not currently able to be measured adequately and were not included in the analysis.[9] Costs and benefits were discounted at a 3% annual rate to account for their decreased value over time.[9] The model was validated by comparing the life expectancy of a 50-year-old woman at average cardiac and breast cancer risk who selects no therapy from the simulation (31.68 years) to estimated life expectancy of a 50-year-old US woman from the National Center for Health Statistics (31.7 years).[10]

Transition probabilities for disease incidence, disease mortality, and the impact of alternative therapies on disease incidence are shown in Tables 1 and 2. For the base-case analysis, the probability of developing coronary heart disease was that of women with population levels of low-density lipoprotein, total cholesterol, systolic blood pressure, no history of diabetes, smoking, or left ventricular hypertrophy.[11,12] The effect of raloxifene on coronary heart disease was estimated from its impact on total cholesterol and high-density lipoprotein in the base-case analysis and its impact on low-density lipoprotein in sensitivity analyses.[12,13] The effect of HRT on coronary heart disease was taken from a large, prospective cohort study in the base-case and its impact on lipids in sensitivity analyses.[1,13] Consistent with the results of a recent randomized controlled trial of HRT in women with coronary heart disease (HERS), HRT was assumed not to affect mortality after a diagnosis of coronary heart disease.[8] Estimated mortality after a diagnosis of coronary heart disease was adjusted for the recent substantial decrease in coronary heart disease case fatality among US women.[14,15]

The relative risk of hip fracture in the base-case anal-

Table 2. Effect of Interventions on Disease Incidence

	Relative risk	Sensitivity analysis range	Source(s) (references)
HRT			
Coronary heart disease	0.56	0.3–1.0	1
Hip fracture	0.53	0.3–1.0	2
Vertebral fracture	0.53	0.3–1.0	2
Breast cancer	1.35	1.0–2.0	3
Endometrial cancer	1.00	1.0–6.0	30
Thromboembolism	2.10	1.0–7.8	29
Raloxifene			
Coronary heart disease	0.87	0.5–1.0	5, 6
Hip fracture	0.93	0.5–1.0	5
Vertebral fracture	0.67	0.5–1.0	7
Breast cancer	0.24	0.1–1.0	4
Endometrial cancer	1.00	1.0–6.0	4
Thromboembolism	3.10	1.0–6.2	4

HRT = hormone replacement therapy.

ysis was determined from the effect of raloxifene on bone mineral density, and the point estimate from the MORE study was examined in sensitivity analyses.[4,5] Vertebral fractures were assumed to affect costs and quality of life but not life expectancy. The effect of HRT on vertebral fracture was assumed to be equal to its effect on hip fractures. Although HRT was assumed not to increase the risk of endometrial cancer in the base-case analysis, increases in endometrial cancer risk were examined in sensitivity analyses. Mortality from other causes was obtained by subtracting mortality from the outcomes included in the model from all-cause mortality rates.[10]

Cost and utility model parameters are shown in Table 3. Direct medical costs included average wholesale medication acquisition costs for HRT and raloxifene (obtained from the Red Book[16]) and costs of medical care for health outcomes (obtained from the published literature). All costs were adjusted to year 2000 dollars using the medical component of the Consumer Price Index.[17] Quality-adjusted life expectancy was calculated from utility values assigned to each health state in the model by 30 local internists. Because of the limitations of using physician utilities as proxies for patient utilities, sensitivity analyses were conducted using the range of relevant health state patient utilities reported in the literature.[9] Future benefits, events, and costs were adjusted for time effects using a 3% discount rate.[9]

Because of limited randomized trial data and concerns about the generalizability of the data that are available, sensitivity analyses were performed to assess the impact of uncertainty of data inputs and to provide information for women with different risk profiles. One- and two-way sensitivity analyses were conducted to assess the impact of alternative assumptions about: 1) effectiveness of HRT in primary prevention of coronary heart disease; 2) effectiveness of raloxifene in primary prevention of coronary heart disease; 3) magnitude of breast cancer risk associated with HRT; 4) effectiveness of raloxifene in primary prevention of breast cancer; and 5) existence of any residual increase in risk of endometrial cancer with estrogen/progesterone regimens. For each sensitiv-

Table 3. Costs and Utilities

	Costs ($)		Utilities
	Estimate	Source(s) (references)	Estimate
Coronary heart disease			
First y	3690		0.665
Subsequent y	1155	11, 31, 32	0.871
Death	12,995		0.274
Breast cancer			
First y	12,775		0.546
Subsequent y	1400	33	0.864
Death	22,835		0.192
Hip fracture			
First y	18,403		0.613
Subsequent y		34	0.915
Death	20,500		
Vertebral fracture			
First y	4980		0.704
Subsequent y			0.858
Death		35	
Endometrial cancer			
First y	12,724		0.577
Subsequent y	881		0.881
Death	21,265	36	0.192
Thromboembolism			
First y	5790		0.682
Subsequent y		37	0.925
Death	10,085		
Raloxifene (annually)	740	16	
HRT (annually)	270		

Abbreviation as in Table 2.

Table 4. Results

Time frame	Strategy*	Δ LE	Δ QALY	Δ Cost ($)	Incremental CE ($/QALY)
Long-term therapy	**HRT** vs no therapy	0.65	1.75	3802	2173
	Raloxifene vs no therapy	0.71	1.32	12,968	9824
	Raloxifene vs **HRT**	0.06	−0.43	9166	HRT dominant†
5-y therapy	**HRT** vs no therapy	0.16	0.45	2259	5020
	Raloxifene vs no therapy	0.28	0.52	4851	9328
	Raloxifene vs HRT	0.12	0.07	2592	37,029
10-y therapy	**HRT** vs no therapy	0.36	0.90	3834	4260
	Raloxifene vs no therapy	0.47	1.03	8123	7886
	Raloxifene vs HRT	0.11	0.13	4289	32,992

LE = life expectancy; QALY = quality-adjusted life years; CE = cost-effectiveness. Other abbreviation as in Table 2.
* Strategy in bold represents the most cost-effective alternative.
† Both more effective and less costly.

ity analysis, threshold values were identified where alternative regimens exceeded $50,000 per quality-adjusted life year and where alternatives no longer increased life expectancy. The range of values was taken from the widest 95% confidence interval in published studies or from the range of reasonable values developed through discussion with local experts. Because of uncertainty in the measurement of costs and utilities, the range for sensitivity analyses always included estimates from at least half to twice the base-case value.

RESULTS

Compared with no treatment, both lifetime HRT and raloxifene therapy increase life expectancy and quality-adjusted life expectancy and are cost-effective for a 50-year-old postmenopausal woman at average risk for coronary heart disease and breast cancer. HRT provides an additional 0.65 discounted years of life expectancy at a net lifetime discounted cost of $3802 ($5849 per additional year of life); raloxifene an additional 0.71 discounted years of life expectancy at a net lifetime discounted cost of $12,968 ($18,265 per additional year of life) (Table 4). Because HRT reduces hip and vertebral fractures more than raloxifene therapy and fractures impact quality of life more than mortality, HRT increases quality-adjusted life years more than raloxifene therapy (gain of 1.75 versus 1.32 quality-adjusted life years) at a lower cost ($2173 versus $9824 per additional quality-adjusted life year). Thus, when choosing between lifelong raloxifene therapy and HRT, HRT is the dominant alternative (more effective and less costly). However, for shorter durations of therapy (ie, 5 or 10 years after menopause at age 50), raloxifene results in greater increase in life expectancy and quality-adjusted life expectancy than HRT at a cost of less than $50,000 per additional quality-adjusted life year.

As the estimated effectiveness of HRT for primary prevention of coronary heart disease declines, the relative effectiveness and cost-effectiveness of HRT decreases (Table 5). If the effect of HRT on lipid profiles

Table 5. Cost-Effectiveness of Long-Term Therapy According to RR of Coronary Heart Disease With HRT

RR	Strategy*	Δ QALY	Δ Cost ($)	Incremental CE ($/QALY)
0.5	**HRT** vs no therapy	1.92	3668	1909
	Raloxifene vs no therapy	1.32	12,969	9825
	Raloxifene vs **HRT**	−0.60	9301	HRT dominant†
0.7	**HRT** vs no therapy	1.36	4109	3026
	Raloxifene vs no therapy	1.32	12,969	9825
	Raloxifene vs **HRT**	−0.04	8860	HRT dominant†
0.9	**HRT** vs no therapy	0.82	4531	5519
	Raloxifene vs no therapy	1.32	12,969	9825
	Raloxifene vs HRT	0.50	8438	17,002
1.0	**HRT** vs no therapy	0.56	4735	8429
	Raloxifene vs no therapy	1.32	12,969	9825
	Raloxifene vs HRT	0.76	8234	10,900

RR = relative risk. Other abbreviations as in Tables 2 and 4.
* Strategy in bold represents the most cost-effective alternative.
† Both more effective and less costly.

Table 6. Effect of Predicted Lifetime Breast Cancer Risk on Cost-Effectiveness of Long-Term Therapy

Breast cancer risk	Strategy*	Δ QALYs	Δ Cost ($)	Incremental CE ($/QALY)
10%	**HRT** vs no therapy	1.75	3802	2173
	Raloxifene vs no therapy	1.32	12,968	9825
	Raloxifene vs **HRT**	−0.43	9166	HRT dominant†
15%	**HRT** vs no therapy	1.47	4087	2767
	Raloxifene vs no therapy	1.66	12,294	7406
	Raloxifene vs HRT	0.19	8207	43,056
30%	**HRT** vs no therapy	0.83	4730	5715
	Raloxifene vs no therapy	2.57	10,538	4100
	Raloxifene vs HRT	1.74	5808	3830
65%	HRT vs **no therapy**	0	5434	No therapy dominant†
	Raloxifene vs no therapy	4.02	7641	1900
	Raloxifene vs HRT	4.02	2207	549
80%	HRT vs **no therapy**	−0.19	5536	No therapy dominant†
	Raloxifene vs no therapy	4.43	6777	1530
	Raloxifene vs HRT	4.62	1241	269

Abbreviations as in Tables 2 and 4.

* Strategy in bold represents the most cost-effective alternative.

† Both more effective and less costly.

from the Postmenopausal Estrogen/Progestin Interventions trial is used to estimate its impact on coronary heart disease, HRT decreases coronary heart disease risk by 25% (relative risk [RR] 0.75) and remains more effective and less expensive than raloxifene. If HRT does not reduce coronary heart disease risk, raloxifene becomes the preferred alternative with an incremental cost-effectiveness relative to HRT of $10,900 per quality-adjusted life year.

As the estimated effectiveness of raloxifene for primary prevention of coronary heart disease increases, raloxifene becomes relatively more effective and cost-effective than HRT. If raloxifene reduces coronary heart disease incidence by 30% (RR 0.70), raloxifene and HRT result in an equal gain in quality-adjusted life years. If the effect of raloxifene on coronary heart disease is equal to that estimated in the base-case for HRT (RR 0.5), raloxifene is the more cost-effective alternative.

As the risk of breast cancer from HRT increases, the relative effectiveness and cost-effectiveness of HRT compared with raloxifene decrease. However, HRT is both more effective and less expensive than raloxifene therapy across the range of published estimates (RR 0.9–1.74). If HRT does not increase the risk of breast cancer, use of HRT results in an increase of 0.85 quality-adjusted life years compared with use of raloxifene at a cost saving of $10,900.

As raloxifene becomes more effective in primary prevention of breast cancer, it becomes relatively more effective and cost-effective than HRT. If raloxifene reduces the incidence of breast cancer by 90% (RR 0.1), raloxifene results in a gain in 1.66 quality-adjusted life years compared with no therapy. However, if one assumes coronary heart disease risk reduction from HRT, this gain in quality-adjusted life expectancy is still less than that seen with HRT. If raloxifene is less effective in primary prevention of breast cancer than estimated in the base-case analysis (RR 0.36 or higher), the relative benefit of HRT further increases.

The risk of endometrial cancer from HRT has little substantive effect on the relative benefit of HRT. If HRT increases the risk of endometrial cancer four-fold (RR 4.0), the incremental gain in quality-adjusted life years for HRT compared with raloxifene therapy falls to 0.07, but HRT remains both more effective and less expensive.

The relative benefit of these therapies depends upon a woman's risk of coronary heart disease, osteoporosis, and breast cancer. Because the benefit of HRT in reducing coronary heart disease and osteoporosis risk is believed to be substantially greater than that of raloxifene, HRT remains the more effective and less expensive alternative for women at increased risk of coronary heart disease and osteoporosis. However, increases in breast cancer risk have a significant impact on the relative benefit of raloxifene and HRT (Table 6). If a woman has a 40% increase over the estimated population lifetime breast cancer risk of 10% (ie, lifetime risk of 14%), raloxifene results in an equal gain in quality-adjusted life expectancy as HRT, and HRT is no longer the dominant alternative. If a woman has a 50% increase in breast cancer risk (ie, lifetime breast cancer risk of 15% or higher), raloxifene becomes the more cost-effective alternative.

Variation in the estimates of costs, utilities, and discount rates has little substantive effect on which alternative therapy is preferred. If the cost of raloxifene falls to $175 per year, raloxifene becomes the less costly alternative ($12,496 versus $12,518). However, HRT still results in a greater gain in quality-adjusted life expectancy with an incremental cost-effectiveness ratio of $51 per quality-adjusted life year compared with raloxifene. HRT remains the dominant or cost-effective alternative for a woman at average coronary heart disease and breast cancer risk across the ranges of costs examined for HRT, coronary disease, breast cancer, osteoporosis, endometrial cancer, or thromboembolism. Furthermore, although the relative benefit of HRT decreases as the discount rate decreases, if neither costs nor life years are discounted, HRT remains the preferred option, with an incremental cost-effectiveness ratio of raloxifene compared with HRT of $882,896 per quality-adjusted life year.

Although the relative benefit of HRT decreases as the utility estimates for coronary heart disease and osteoporosis increase and the estimates for breast cancer decrease, HRT remains the dominant or cost-effective alternative across the range of utility estimates examined. Because HRT reduces menopausal symptoms whereas raloxifene does not, and this issue may be particularly relevant for women taking therapy for only 5 or 10 years after menopause, we examined the effect of an improvement in utility with HRT compared with raloxifene for these time frames. For short-term therapy, if the model assumes even modest benefit in quality of life from HRT compared with raloxifene (absolute increase of 2% or higher), HRT is both more effective and less expensive than raloxifene therapy for 5- to 10-year courses of therapy.

DISCUSSION

Because of the availability of alternative hormonally active therapies that differ in their impact on coronary heart disease, breast cancer, and osteoporotic fracture, and increasing controversy about the effects of HRT on coronary heart disease, we performed a decision analysis to estimate the clinical (life expectancy and quality-adjusted life expectancy) and economic (incremental cost-effectiveness) impact of HRT and raloxifene in postmenopausal women. Assuming the benefit of HRT on coronary risk reported in observational studies and the benefit of raloxifene on coronary risk extrapolated from its effects on lipids, both long-term HRT and long-term raloxifene increase both life expectancy and quality-adjusted life expectancy in 50-year-old postmenopausal women at average risk for coronary heart disease and breast cancer. Because HRT increases quality-adjusted life expectancy more than raloxifene, and raloxifene is more costly than HRT, HRT is the dominant (more effective and less costly) alternative in this setting. Thus, despite raloxifene's apparent reduction in breast cancer incidence, long-term HRT remains the most cost-effective therapy for women at average breast cancer risk seeking treatment to increase their quality-adjusted life expectancy after menopause.

The relative benefits of raloxifene and HRT depend upon a woman's breast cancer risk. For a woman with a predicted lifetime 50% increase in breast cancer risk (ie, lifetime risk of 15% or higher), raloxifene is a cost-effective alternative to HRT, resulting in a greater increase in quality-adjusted life expectancy at an incremental cost of less than $50,000 per quality-adjusted life year. The most widely used and validated model for individual breast cancer risk prediction is the Gail model.[18,19] Gail model software can be obtained from the National Cancer Institute at 1-800-4CANCER or http://cancertrials.nci.nih.gov/forms/CtRiskDisk.html. If using a software program is not feasible, certain breast cancer risk factors (one or more first-degree relatives with breast cancer, one or more prior breast biopsies, history of atypical hyperplasia on a breast biopsy, and carrying a mutation in *BRCA1* or *BRCA2*) consistently convey an RR of breast cancer over 1.5 and can be used to identify women who have a 15% or greater lifetime risk of breast cancer.[19]

The relative benefits of raloxifene and HRT also change significantly with alternative assumptions about the effects of HRT on coronary heart disease risk. If HRT proves to reduce the risk of a first coronary heart disease event by less than 20%, long-term raloxifene becomes the more cost-effective alternative for all women. If the effects of both HRT and raloxifene are extrapolated from changes in lipids, HRT remains the more cost-effective alternative.[5,13] These results provide evidence to help clinicians interpret and implement recent American Heart Association guidelines that suggest decisions about HRT in women without cardiovascular disease "should be based on established noncoronary benefits and risks, possible coronary benefits and risks, and patient preference."[20]

For women interested in pharmacologic therapy for 5 or 10 years after menopause, raloxifene is associated with a greater increase in life expectancy and quality-adjusted life expectancy than HRT at a cost of less than $50,000 per quality-adjusted life year. A woman's risk of death from breast cancer compared with her risk of death from coronary disease and osteoporosis is relatively greater at younger than older ages. Thus, raloxifene's reduction of breast cancer risk has its greatest impact in the years immediately after menopause. How-

ever, the beneficial effect of HRT on menopausal symptoms was not included in this analysis. Even a relatively small symptomatic benefit of HRT relative to raloxifene results in a greater increase in quality-adjusted life years with short-term HRT than with short-term raloxifene.

These results extend prior research in this area. Previous decision analyses without discounting have found HRT to increase life expectancy by 0.5 to 1 year in average-risk women.[21–24] In this analysis, HRT increased life expectancy by 1.0 years in the absence of discounting. One cost-effectiveness analysis also found HRT to be cost-effective compared with no therapy.[21] A recently published decision analysis of alendronate, raloxifene, and HRT found that raloxifene increased life expectancy more than HRT for women at high breast cancer risk and low coronary heart disease risk.[24] However, this prior analysis did not include the recent data about the benefit of raloxifene on breast cancer risk in the base-case analysis or the effects of raloxifene and HRT on vertebral fractures or thrombosis. Furthermore, the current study is the first to assess the comparative economic impact of alternative therapies.

The current study has several limitations. We chose to focus on hormonally active options for postmenopausal women because these options have many competing effects, making a decision analysis particularly valuable. We did not include the many other options for prevention of osteoporosis, coronary disease, and breast cancer that have a single main effect (eg, statins, alendronate), and that may be even more effective than either HRT or raloxifene for a specific complication of hormonal deficiency. However, deciding between options for prevention of a single disorder is potentially less complex, and including all options would make the current analysis difficult to use. Because both HRT and raloxifene have side effects, and an extensive literature search found no evidence that patient adherence differs between the therapies, we did not include the effects of noncompliance in the model. In addition, for many of the model parameters, only limited data are currently available. For example, data on the impact of raloxifene on breast and endometrial cancer come from a single large clinical trial.[4] Although we used the best available evidence for each model parameter estimate, uncertainty is inevitable (eg, effect of HRT on coronary heart disease). In this setting, sensitivity analyses were used to understand the impact of the ranges of uncertainty and provide an important context for understanding the base-case results.

Postmenopausal women now have several options to reduce their long-term risk of coronary heart disease, osteoporosis, and breast cancer. This analysis suggests that for the great majority of postmenopausal women without a major breast cancer risk factor, long-term HRT remains the dominant alternative, resulting in a greater increase in quality-adjusted life expectancy at a lower cost. However, long-term raloxifene therapy is a cost-effective alternative for postmenopausal women at significantly increased risk of breast cancer and is a cost-effective alternative for women with average breast cancer risk who will not take HRT. Until the results of large scale randomized trials of HRT as primary prevention become available, women and physicians continue to face difficult decisions about postmenopausal therapy. This analysis provides important evidence to make more informed decisions and may make counseling postmenopausal women a little easier.

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Short Communication

Factors Associated with Decisions about Clinical *BRCA1/2* Testing[1]

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Abstract

Testing for mutations in *BRCA1* and *BRCA2* can provide important information about breast and ovarian cancer risk to a small but identifiable subgroup of women. Women who test positive for a *BRCA1/2* mutation can pursue more aggressive cancer surveillance and prevention regimens. Among families with known mutations, women who test negative may avoid unnecessary interventions. Currently, little is known about the factors associated with the use of clinical *BRCA1/2* testing. The objective of this study was to determine the factors associated with decisions about clinical *BRCA1/2* testing among women undergoing clinical *BRCA1/2* counseling through a retrospective cohort study of women who participated in a university-based clinic offering breast cancer risk assessment, genetic counseling, and *BRCA1/2* testing between January 1996 and April 1998. From the 251 eligible women who responded to a follow-up survey, 125 (50%) had undergone or were undergoing *BRCA1/2* testing, 86 (34%) had decided not to undergo testing, and 40 (16%) were undecided about testing. After multivariate adjustment, we found that women who chose to undergo *BRCA1/2* testing were more likely to have a known familial mutation [odds ratio (OR), 7.46; 95% confidence interval (CI), 0.97–62.16], more likely to be Ashkenazi Jewish (OR, 6.37; 95% CI, 2.68–15.12), more likely to want cancer risk information for family members (OR, 1.93; 95% CI, 0.99–4.14), more likely to want information about ovarian cancer risk (OR, 1.69; 95% CI, 1.18–3.69), and less likely to be concerned about insurance or job discrimination (OR, 0.45; 95% CI, 0.21–0.94). These associations were also found in the subgroup of women with a predicted probability of a *BRCA1* mutation of ≥5%. Our study suggests that approximately half of eligible women choose to undergo clinical *BRCA1/2* testing after participating in counseling. Women who have the highest risk of carrying a mutation, and thus the greatest probability of gaining some useful information from the test results, are most likely to undergo testing. Women who undergo testing are also more interested in ovarian cancer risk information and less concerned about job and insurance discrimination.

Introduction

Mutations in the cancer susceptibility genes *BRCA1* and *BRCA2* are associated with a significantly increased lifetime risk of breast and ovarian cancer (1, 2). Although interest in genetic testing for cancer susceptibility has grown quickly in the medical community, deciding about *BRCA1/2* testing remains a potentially complex and difficult process.

The primary benefit of *BRCA1/2* testing is the information that can be gained about individual and familial breast and ovarian cancer risk. This information may have significant implications for decisions about cancer surveillance and cancer prevention (3, 4). The limitations and risks of *BRCA1/2* testing are complex (4–6). Currently available options for cancer surveillance and prevention have limited efficacy and/or involve significant trade-offs (4). Furthermore, the cancer risk information gained from testing is limited in most contexts. Outside of families with known mutations, most women test negative and have little change in their predicted risk of breast or ovarian cancer (3). For these women, testing may be unlikely to affect their surveillance or risk reduction regimens. The adverse psychological consequences of positive or negative tests and employment, social, or insurance discrimination are often cited as potential drawbacks to undergoing *BRCA1/2* testing (5, 6). In addition, full *BRCA1/2* testing currently costs over $2,500, and insurance coverage is variable (7).

Currently, little information is available regarding the uptake of *BRCA1/2* testing in a clinical setting or the reason women decide against undergoing testing. To date, most studies have focused on high-risk families offered testing through research protocols (8, 9). The aims of our study were to determine the proportion of women who undergo *BRCA1/2* testing and the factors associated with decisions about *BRCA1/2* testing among women undergoing *BRCA1/2* counseling at a clinical breast cancer risk assessment program that offers genetic testing as a clinical service.

Materials and Methods

Study Setting. The University of Pennsylvania BCREP[3] is a multidisciplinary clinical program that provides breast cancer risk assessment, genetic counseling, and genetic testing for *BRCA1/2* mutations. The program has provided clinical testing for *BRCA1/2* mutations to women without cancer since October

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[3] The abbreviation used is: BCREP, Breast and Ovarian Cancer Risk Evaluation Program.

1996. Although research testing is offered selectively based on eligibility criteria, clinical testing is provided to any individual who chooses to undergo testing after participating in genetic counseling. Women with an estimated probability of a *BRCA1/2* mutation of <5% are counseled that they are unlikely to gain information from testing. During this study, estimates of the probability of *BRCA1* mutation were provided using a prediction model developed by Couch *et al* (10). A similar *BRCA2* prediction model did not exist at the time of the study. On the basis of the population genetics of *BRCA1/2*, non-Ashkenazi women were told their risk of *BRCA2* mutation was about half that of *BRCA1*, whereas Ashkenazi women were told their risk of *BRCA2* mutation was equivalent to that of *BRCA1* (11). Women who were not considering undergoing *BRCA1/2* testing at the time of their visit to BCREP received individualized information about breast and ovarian cancer risk and surveillance recommendations but did not undergo full pretest genetic counseling.

Study Design and Subject Selection. A total of 518 individuals participated in the BCREP between January 1995 and April 1998. Women who had previously requested not to participate in further research ($n = 22$) and men ($n = 6$) were excluded. In October 1998, all of the eligible subjects ($n = 490$) were mailed a questionnaire, a letter, and a stamped, addressed envelope. Subjects who did not respond were mailed two reminder letters, including questionnaires. The study protocol was approved by the Institutional Review Board of the University of Pennsylvania.

Data Collection. To identify factors that were associated with decisions about genetic testing, four focus groups of women ($n = 16$) who had participated in the BCREP were held. In each group, women were asked to list all of the issues that had influenced their decision about genetic testing. A questionnaire was developed that asked respondents to rate the importance of each factor identified in the focus groups on a four-point Likert response scale (very important, moderately important, a little important, and not at all important). These factors are listed in Table 2. In addition, the questionnaire asked subjects if they had already undergone testing, had decided to undergo testing in the future, were undecided about testing, or had decided not to undergo testing. Sociodemographic characteristics and family history of breast cancer were obtained from clinical records.

Statistical Analysis. Predicted lifetime risks of breast cancer for subjects without a diagnosis of breast cancer were calculated from prediction tables developed by Claus *et al* (12). Predicted risks of *BRCA1* mutation for the BCREP population were calculated from tables developed by Couch *et al.*(10). Because these risks had skewed distributions, Wilcoxon's rank-sum test was used in confirmatory analyses. For the primary analysis, women were characterized by self-report as having decided not to undergo testing (declined testing group) or undergoing/having undergone testing (tested group). Women who were undecided about testing were excluded. Associations between each variable and the testing decision were examined using Wilcoxon's rank-sum test for ordered variables (*i.e.,* importance rated on a four-point scale) and the ordinary χ^2 test for dichotomous variables (*e.g.,* very important *versus* other). Multivariable analyses were conducted using multiple logistic regression. Because of correlations between concerns about health insurance, life insurance, and job discrimination and between the importance of ovarian cancer risk information and the importance of help deciding about prophylactic oophorectomy, composite variables were constructed to represent concern about discrimination from testing and interest in information about ovarian cancer risk. No other significant correlations were identified between variables associated with testing in this sample, including Ashkenazi background and presence of familial mutation. Each variable associated with testing in bivariate analysis at $P \leq 0.10$ was tested for inclusion in the model. The final model included all of the variables whose inclusion altered the odds ratio for another variable by ≥10%. Because of concern that women might perceive the factors that influenced their decisions differently over time and according to their test results, we tested interaction terms for calendar time since counseling and *BRCA1/2* test results. To understand the factors that affected testing decisions among women who had an elevated risk of carrying a mutation, we repeated our analyses in the subgroup of women with a predicted probability of *BRCA1* mutation of ≥5%.

Table 1 Subject characteristics

	Overall ($n = 211$)	Testing ($n = 125$)	Declined testing ($n = 86$)	Two-tailed *P*
Mean age, yrs (range)	44.6 (24–73)	45.8 (24–73)	42.7 (27–73)	0.04
Caucasian (%)	96.8	98.1	94.6	0.21
Ashkenazi (%)	29.9	42.9	13.3	0.0005
College education (%)	73.6	77.6	71.7	0.49
Employed (%)	74.0	74.1	77.3	0.72
Breast cancer (%)	30.9	36.5	22.7	0.04
Known familial mutation	6.2	9.7	1.1	0.04
Predicted breast cancer risk, mean (SD)[a]	0.24 (0.13)	0.26	0.21	0.03
Predicted *BRCA1* risk, mean (SD)	0.18 (0.20)	0.24 (0.23)	0.10 (0.07)	<0.0005

[a] Among women without a breast cancer diagnosis.

Results

Of the 490 women to whom surveys were mailed, 10 women had died, and 36 women had moved. A total of 353 women returned completed surveys for a response rate of 80%. Nonresponders did not differ from responders in age, predicted risk of breast cancer, or predicted risk of a *BRCA1* mutation in the family ($Ps > 0.1$). Eighteen women who were not considering undergoing *BRCA1/2* testing at the time of their visit, 76 women who were seen before *BRCA1/2* testing was offered to women without cancer outside of a research protocol, and 8 women who pursued testing through a research protocol were excluded from these analyses. Of the remaining 251 eligible women, 125 (50%) women had undergone *BRCA1/2* testing or were undergoing testing, 86 (34%) had decided not to undergo testing, and 40 (16%) were undecided about testing (including 14 women who had a family member pursuing testing).

The characteristics of women who underwent testing and women who decided not to undergo testing are reported in Table 1. Women who underwent testing were older and more likely to be Ashkenazi Jewish, to have a diagnosis of breast cancer, and to have a known familial *BRCA1* or *BRCA2* mutation than women who declined testing. Women who underwent testing had a slightly higher risk of breast cancer and a substantially higher risk of carrying a *BRCA1* mutation than women who declined testing.

Women who underwent testing were significantly more likely to rank several potential benefits of testing as very important in their decision (Table 2). These benefits included providing cancer risk information for family members, learning information about ovarian cancer risk, and obtaining help in

Table 2 Benefits, risks, and limitations of *BRCA1/2* testing (reported as the percentage of subjects rating a factor very important)

Factors	Testing (n = 125)	Declined testing (n = 86)	Two-tailed P
Learning about my breast cancer risk	76.3	73.8	0.69
Learning about my ovarian cancer risk	76.1	57.5	0.005
Providing information for family members	75.8	56.3	0.003
Help deciding about prophylactic mastectomy	38.7	21.5	0.01
Help deciding about prophylactic oophorectomy	59.1	29.5	0.0001
Help deciding about estrogen replacement	29.9	28.8	0.89
Desire to be reassured if test was negative	73.9	69.7	0.52
Concern about my anxiety if test was positive	36.7	46.3	0.17
Fear of health insurance discrimination	36.1	47.1	0.11
Fear of life insurance discrimination	28.1	42.2	0.04
Fear of job discrimination	12.4	27.7	0.006
Cost of the test	22.3	22.9	0.74
My doctor's recommendation	39.3	32.1	0.30
My family's recommendation	30.7	30.0	0.96
Desire to help advance research	46.3	40.0	0.37

Table 3 Adjusted associations with undergoing testing (n = 169)

	OR[a]	95% CI[b]	Two-tailed P
Familial mutation	7.46	0.97–62.16	0.06
Ashkenazi background	6.37	2.68–15.12	0.0005
Importance of			
Information for family members	1.93	0.99–4.14	0.05
Information about ovarian cancer risk	1.69	1.18–3.69	0.009
Fear of insurance discrimination	0.45	0.21–0.94	0.03

[a] OR, odds ratio.
[b] CI, confidence interval.

deciding about prophylactic oophorectomy and prophylactic mastectomy. Conversely, concerns about life insurance and job discrimination were more likely to be considered very important by women who declined testing. After multivariable analyses, Ashkenazi background, known familial mutation, fear of insurance discrimination, importance of information for family members, and importance of information about ovarian cancer risk remained associated with use of testing (Table 3). No interaction was found between the effects of these factors and calendar time since counseling or *BRCA1/2* test results ($Ps > 0.2$).

Among the subgroup of women (n = 206) with a predicted probability of a *BRCA1* mutation of ≥5%, 60 (29%) women had declined testing, 116 (56%) women had chosen to undergo testing, and 30 (15%) women were undecided (including 11 women who had a family member pursuing testing). After multivariable adjustment, there were no substantial differences between the associations with testing decisions in this subgroup and those associations found in the entire sample (data not shown).

Discussion

This study suggests that approximately two-thirds of women considering *BRCA1/2* testing at the time of their visit to a clinical cancer risk evaluation program decide to undergo testing after participating in counseling. Women who undergo testing are at higher risk of carrying a *BRCA1* mutation, more likely to want information about ovarian cancer risk for themselves and about breast and ovarian cancer risk for family members, more likely to be Ashkenazi Jewish, more likely to have a known familial mutation, and less likely to be concerned about insurance or job discrimination. The association with risk of *BRCA1* mutation is present whether measured by predicted probabilities, the presence of familial mutation, or the presence of risk factors, *i.e.,* Ashkenazi Jewish heritage.

The associations between the risk of carrying a mutation, a known familial mutation, and gaining risk information for family members and decisions about *BRCA1/2* testing are reassuring. Most experts agree that *BRCA1/2* testing should be targeted to women who are most likely to gain useful information from testing (13, 14). Women at higher risk of carrying a mutation are more likely to be found to carry a mutation, more likely to gain useful information, and should be more likely to decide to get tested. Women with a familial mutation will also gain more information from a negative test, because the cause of their familial predisposition has been identified. Furthermore, because of the potential implications of genetic testing for family members, more information is gained from *BRCA1/2* testing when the results are salient to other family members.

The relatively greater importance of ovarian cancer risk information is likely to be multifactorial. First, prophylactic oophorectomy may appeal to more women than prophylactic mastectomy, both because prophylactic mastectomy is a more extensive and potentially disfiguring procedure and because substantially more evidence exists supporting the efficacy of breast cancer surveillance than that of ovarian cancer surveillance (15–17). Second, for the majority of women concerned about their increased breast cancer risk at the time they seek *BRCA1/2* counseling, finding a *BRCA1/2* mutation only confirms their belief in their increased risk. The information that testing may bring about ovarian cancer risk may seem like the bigger change. Third, *BRCA1/2* testing was the only method available to assess individual ovarian cancer risk at the time of this study, whereas several models were available to predict breast cancer risk (18).

Although there is little evidence suggesting that insurance discrimination is occurring at present, the association between fear of insurance or job discrimination and decisions about *BRCA1/2* testing is disconcerting. Because genetic information cannot be taken back once received, many women are reluctant to pursue testing without assurance that discrimination could not occur in the future. This situation is particularly paradoxical if women who would have been found to carry a mutation and taken steps to lower their cancer risk decline testing because of fear of insurance discrimination. Information gained from *BRCA1/2* testing that results in women choosing interventions that lower their risk of cancer is good for everyone concerned, including life and health insurers.

This study both extends and supports the findings of prior studies of decisions about *BRCA1/2* testing. Prior studies using hypothetical scenarios generally found a majority of women reported interest in testing, and interest in testing was higher among women with a higher perceived risk of carrying a mutation, greater concerns about cancer risk, and more interest in getting information for family members (19–23). Conversely, studies of research family members found that <50% of participants requested their genetic test results; however, participants requesting results also rated the benefits of testing

more highly, knew more about *BRCA1* testing, and had more first-degree relatives with breast cancer (8, 9).

Because this study was conducted retrospectively, the decision about testing may have influenced the perceptions and reporting of the factors that were important in that decision. We cannot determine to what degree women may have adopted beliefs after they made their decision to support or justify their behavior (24). In addition, the factors that women felt were most important in their decision about *BRCA1/2* testing may have changed over time. Establishing a single time when decisions are made about testing is difficult. In our sample, almost a fifth of women were still undecided about testing up to 2 years after counseling. The time point for this study was selected to minimize the number of women who were undecided about testing while maintaining reasonable proximity to the date of counseling. Although the cost of testing was not an important factor in our study, our sample was highly educated and thus likely to be relatively affluent. Cost may be an important barrier to testing in less affluent populations. Finally, the generalizability of these results to women currently participating in similar programs is unknown.

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